Acta Paediatrica

Vol. 44 · May 1955 · No 3

UNIVERSITY OF MICHIGAN
MAY 31 1956
MEDICAL LIBRARY

INDEX

Non-Rachitic Craniotabes 185
Bo S. V. Bille

Three Months' Colic 203
R. S. Illingworth

Nephrogenic Diabetes Insipidus in Children 209
Åke Ellborg and Hans Forssman

Fatal Tuberculosis From BCG Vaccination 219
S. Falkmer, A. Lind and L. Ploman

Should Mass-Vaccination With BCG Be Discontinued in Scandinavia? . . . 237
Arvid Wallgren

Acute Cerebellar Ataxia in Children 254
G. Berglund, H. O. Mossberg and B. Rydenstam

La Sténose Hypertrophique de Pylore chez le Nourrisson Prématuré 263
G. Van Ooteghem

Auricular Flutter in Infancy 272
B. Landtman and Eila Kassila

Osteogenesis Imperfecta Associated with Ehlers-Danlos Syndrome 279
Axel Biering and Torben Iversen

Hemihypertrophy and Wilms's Tumour 287
Stig-Ivar Björklund

Book Review 292

Subscription Price 45 Swedish crowns. Single copies 10 Swedish crowns.
Published by ALMQVIST & WIKSELLS BOKTRYCKERI AB, Uppsala, Sweden.

ACTA PÆDIATRICA

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Acta Pædiatrica 44: 185—202. May 1955

From the Children's Hospital, Sundsvall, Sweden (Head: GERT VON SYDOW, M.D.)

Non-rachitic Craniotabes

by BO S. V. BILLE

This clinical study was undertaken to shed further light upon the occurrence and pathogenesis of craniotabes, which has been known in the literature for more than a century by, among others, the following names: craniomalacia, cranial softening, vertex softening, osteoporosis, and Kuppenweichschädel.

Historical Review

VON ELSÄSSER was the first to describe craniotabes in the literature, when, in 1843, he published his work "Der weiche Hinterkopf", where he described 31 infants with postnatal craniotabes, which he called the "rickets of infancy". He supposed that the localization was due to pressure of the brain on the back of the skull in a horizontal position.

On the other hand, FRIEDLEBEN, in 1860, considered craniotabes as physiological and supposed that the cause was the external pressure on the skull in the horizontal position resulting in incomplete ossification. Later on, these two main theories regarding the origin of craniotabes as rachitic or physiologic were to oppose each other as they do to-day.

In several studies during the period from 1880 to 1884, KASSOWITZ maintained that all forms of craniotabes are rachitogenic and that rickets is congenital. He also was the first to introduce the term "congenital craniotabes". He found that craniotabes occurred more frequently during winter than summer and more frequently among urban populations than among rural.

BOHN, in 1885, as well as REHN, in 1883, maintained that there are two forms of craniotabes: a congenital, non-rachitic, type which is thought to be due to deficient ossification, and which disappears before the age of two months; and a rachitic one, which appears later on.

WIELAND also, in 1908, distinguished two forms of craniotabes: the congenital form, which occurs in about 20 per cent of all newborn infants, is localized to the vertex (Kuppenweichschädel) and is due to the pressure of the rapidly growing brain; and the rachitic one, a softening of former hard bone, appearing after the first six weeks of life.

In 1921, HUGHES maintained that congenital craniotabes is caused by an external pressure of the lower uterine segment and the pelvic bones and internal pressure from the growing brain. He also noted a seasonal variation and considered postnatal craniotabes to be a fresh manifestation of the congenital form, both caused initially by mechanical pressure, even if decalcifying factors could not be excluded.

ABELS and KARPLUS stated, in 1927, that congenital craniotabes was not physiologic but pre-rachitic and caused by mechanical pressure of the maternal pelvis, combined with certain constitutional factors and possibly also with maternal dietary deficiency as a contributory factor.

HÖJER, in 1926, reported 70 cases of craniotabes (none of the infants examined before the age of one month), of which 23 also showed rachitic changes. Among the 47 non-rachitic cases there was no predominance of sex and no seasonal variation. He thought that just as the rachitic craniotabes was becoming more uncommon, one might suppose that the physiologic craniotabes would be more often observed.

JUNDELL, in 1931, found in his study that the administration of cod liver oil or irradiated ergosterol to mothers and later on to their children could prevent the development of rickets in the children but not of congenital and postnatal craniotabes. He maintained that craniotabes is a physiologic or hypoplastic process.

In 1937, KASAHARA, KAWASHIMA and TOKUYAMA published a report of 3908 children (92.2 per cent breast fed) from Osaka, Japan, where rickets is very unusual. The children were examined during the first year of life. In 8.1 per cent of the total they found postnatal craniotabes, most often among those who were examined at the age of three months, where the frequency of craniotabes was 32.8 per cent. The authors concluded that this craniotabes was not of rachitic origin.

ANDERSEN, ROTHE-MEYER and TUDVAD, in 1948, reported a group of 895 children of whom 87 had rickets (more than twice as many boys as girls) and 173 had postnatal craniotabes (no sex difference). Children growing more rapidly more often developed craniotabes than those growing slowly.

BLOM, in 1950, examined 662 children and found postnatal craniotabes in 12.6 per cent and considered it to be physiological.

The biggest investigations of congenital craniotabes in later years were published by REISS and BODER in 1940 and by BODER in 1949 and 1952. These studies, founded on examinations of 800, 875, and 1425 newborn infants, respectively, of different races, showed predilection of congenital craniotabes for infants below average birth weight, crown-heel measurement and occipito-frontal head circumference as well as for male, first-born and Negro infants. They also found a seasonal variation which they considered to support the conclusion that congenital craniotabes is directly related to the lack of maternal exposure to the sun during pregnancy. They thought the primary factor to be intrauterine pressure effects, with generally deficient bony calcification due to avitaminosis D during pregnancy, or prematurity of the infant, as chief contributory factors.

The Author's Study

A. Congenital Craniotabes

MATERIAL

The material is made up of 1541 live born infants, who were delivered at the Obstetric Department in Sundsvall (Lat. 62° N.) during the year between the 1st of June 1951 and the 31st of May 1952. The mothers came from rural areas, small industrial districts and small towns.

All the children were examined by a pediatrician at least twice during their stay in hospital, first on the day after delivery and then on the day of departure; as a

rule, the sixth day of life. Through careful palpation, the existence of possible softness of skull bones, congenital craniotabes, has been recorded, as well as the degree thereof. Each side of the skull has been examined separately, and unless specified, the degree stated for each case is that of the side where craniotabes is most marked. The extent of craniotabes has been classified as (+), where the bone is only compressible on a small area of a few square centimetres; (++), where the area is bigger, or where the bone is soft at several small places on the same side; and (+++), where the greater part, or the whole parietal bone, is soft (in the most marked cases almost as thin as paper). In practically all cases only the parietal bones were affected, but in a few cases with particularly marked forms of craniotabes, the upper portion of the frontal bone was also involved. The temporal and the occipital bones were not found involved in any case. Slight yielding or rocking of the bones near the fontanels and sutures has not been counted as craniotabes. The classification has had to be very subjective, and therefore it is of value that the majority of the more than 3000 observations has been made by the same investigator.

Statistics

The term "significant" was used to indicate differences having a value (the critical ratio) of three or more times their standard error; "suggestive" to indicate a critical ratio of between two and three; "non-significant" to indicate a critical ratio of less than two.

Results

Breech-born

Hughes and Abels stated that congenital craniotabes never occurs among breech-born infants, and Boder in her material had 50 breech-born infants, none of whom had craniotabes. Neuhaus found one breech-born infant among his 384 cases of congenital craniotabes. Also Toverud and Wieland maintained that congenital craniotabes may occur in infants born by breech presentation.

In this study there were 45 breech-born infants, 22 born of primiparae and 23 of multiparae, and not one of them had congenital craniotabes. During the period between the 1st of June 1952 and the 31st of August 1953, in direct connection with "the investigation year", 55 more infants have been born in breech presentation at the same obstetric department. Of these, one child belonging to a 21-year-old primipara had craniotabes (+++) on the right side. (Further data of child: Duration of pregnancy 280 days, birth weight 3240 g, birth length 52 cm, head circumference 35 cm. Roentgenological examination of the right wrist was normal. Serum calcium 11.4 mg%, serum inorganic phosphorus 7.1 mg%, serum phosphatase 8.5 units. The blood analyses were taken during the day after delivery.) Thus in all, 100 breech-born infants have been examined. In 54 cases the mother was a primipara, and in 46 cases, multiparous. One child of a primipara had unilateral congenital craniotabes.

Caesarean section

Two of the 384 infants with congenital craniotabes, which NEUHAUS described, were delivered by Caesarean section.

In this study, 14 infants have been delivered by Caesarean section, but none of these had congenital craniotabes. The author, however, has examined several children, not included in this material, who were delivered by Caesarean section and who had craniotabes. Often, in these cases, the head had long been pressing against the floor of the pelvis.

Instrumental deliveries

In the study of NEUHAUS, 11.5 per cent of the infants with congenital craniotabes were born by instrumental delivery. He maintained that the high percentage was due to the fact that so many children were born of primiparae. REISS and BODER found no correlation between congenital craniotabes and instrumental delivery.

In this study, 25 children, all of them born of primiparae, had instrumental delivery. Five of these had congenital craniotabes.

Twins

Among 800 infants REISS and BODER had five sets of twins. Only one of these ten children had congenital craniotabes.

In this study there were twenty sets of twins. Of these 40 children, six had congenital craniotabes, in each case being the first-born twin.

Cephalic presentation

1. *Frequency*

In different investigations the frequency of congenital craniotabes varies considerably, which, according to some authors, is due to geographical, racial or social differences. Probably, however, the different results are very often caused by techniques of various investigators in establishing the diagnosis craniotabes and their varying norm of what is to be considered as craniotabes. NEUHAUS himself pointed out that in his material only the most marked forms of craniotabes had been included and he found the low frequency of 2.3 per cent. GARRAHAN found 5.3 per cent; ARLUK, 9.7 per cent; WIELAND, 18.6 per cent; and HUGHES, 21.6 per cent. In a series of more than 800 infants of different races born with cephalic presentation, BODER found congenital craniotabes in 32.9 per cent. Among Negro infants the frequency was still higher. In another series of 535 infants, published later from Mexico City, BODER found congenital craniotabes in only 21.1 per cent.

In the author's study, 1417 infants have been born spontaneously with cephalic presentation and of these, 228 infants or 16.1 ± 0.98 per cent had congenital craniotabes. This group of 1417 infants has been examined more closely.

2. *Birth order*

HUGHES, ABELS and KARPLUS, ARLUK, and others, found a higher frequency of congenital craniotabes in those born of primiparae. BODER found congenital craniotabes in 37.8 per cent of those born of primiparae, and in 30.9 per cent of those born of multiparae. The difference was biggest in the Negro group (59.3 per cent and 37.9 per cent, respectively) and smallest in the Anglo-American group (34.6 per cent and 32.6 per cent, respectively). Again, the incidence of congenital craniotabes showed a tendency to decrease as the infant's birth order increased.

In the author's study, congenital craniotabes has been twice as frequent among first-born infants (24.2 per cent) as among the later born (10.8 per cent). Each of the three degrees of congenital craniotabes was equally distributed among all the first-born infants. The most marked form (+ + +) was found in 31.8 per cent of all congenital craniotabes among the first-born infants. Among those later born the most marked form has been less frequently found than the two slighter forms (+ + and +) or in only 16.1 per cent of all congenital craniotabes in this group of infants. This difference between 31.8 per cent and 16.1 per cent is suggestive with a critical ratio value of 2.84. (Tables 1 and 2.)

3. *Sex*

Several authors (2, 24) found among rachitic children a male predominance of about two to one. With reference to craniotabes, some authors found a similar difference of sex distribution, while others did not find any. LEVINSON in a material of postnatal craniotabes found a predominance of boys and so did BODER in her material of congenital craniotabes.

TABLE 1

Distribution of congenital craniotabes among infants of primipaae and multiparae born with cephalic presentation.

Parity	Type of skull					Total
	Craniotabes				No craniotabes	
	+	+ +	+ + +	Total		
Primiparae	46	46	43	135	424	559
% of total	**8.2**	**8.2**	**7.8**	**24.2**	75.8	100.0
(% of craniotabes) . .	34.1	34.1	31.8	100.0		
Multiparae	40	38	15	93	765	858
% of total	**4.7**	**4.4**	**1.7**	**10.8**	89.2	100.0
(% of craniotabes) . .	43.0	40.9	16.1	100.0		
All infants	86	84	58	228	1189	1417
% of total	**6.1**	**5.9**	**4.1**	**16.1**	83.9	100.0
(% of craniotabes) . .	37.7	36.8	25.5	100.0		

TABLE 2

Distribution of congenital craniotabes in relation to order of birth.

(The infants born with cephalic presentation.)

Order of birth	Total	Craniotabes		Difference	Critical ratio
		No.	%		
I (1st)	559	135	24.2		
				10.9 ± 2.42	4.5
II (2nd)	452	60	13.3		
				5.2 ± 2.1	2.5
III—XII	406	33	8.1		

There was no difference of sex distribution in the author's study; neither among the groups of children born with cephalic presentation, nor those born exclusively of primiparous or multiparous mothers. Not even when separating the 395 first-born infants, who had a cephalic presentation and a birth weight between 3000 g and 3999 g, was there any difference in sex distribution.

4. *Birth weight*

Several investigators found a greater incidence of congenital craniotabes in infants in lower weight groups.

Because congenital craniotabes occurs more frequently in infants born of primiparae than those born of multiparae, and as the weight of the first born is, on the average, lower than that of the others, the author has compared the frequency of craniotabes in different weight groups only among first-born infants.

Comparing the 100 infants with birth weight of 3000 g or below (32.0 per cent of these had congenital craniotabes) with the 232 infants with birth weight of 3500 g or more (19.8 per cent of these had congenital craniotabes), one finds that this difference is statistically suggestive with a critical ratio value of 2.27.

By comparison between other weight groups the author has not found any statistical difference.

5. *Birth length*

NEUHAUS did not find any difference in the frequency of craniotabes in relation to different birth lengths, while REISS and BODER found a predilection for infants below average crown-heel measurement.

Here, too, the author has only examined first-born infants. The crown-heel measurement was carefully taken immediately after delivery and recorded to the nearest cm. The mean length was found to be 51.81 cm.

Comparing the frequency of congenital craniotabes in 320 infants with birth length 51 cm or below (28.8 per cent of these had congenital craniotabes)

with 239 infants with birth length 52 cm or more (18.0 per cent of these had congenital craniotabes), one finds that this difference is statistically significant with a critical ratio value of 3.03.

6. *Head circumference at birth*

Reiss and Boder found an increased frequency of congenital craniotabes among infants with below average occipito-frontal head circumference.

Here, too, the author has only examined first-born infants. The occipito-frontal head circumference was taken immediately after delivery at the prominent part of the brow and the occiput and the measurement was recorded to the nearest cm. The mean head circumference was found to be 34.13 cm.

Comparing the frequency of congenital craniotabes in 468 infants with head circumference 35 cm or below (26.5 per cent of these had congenital craniotabes) with 91 infants with head circumference 36 cm or more (12.1 per cent of these had congenital craniotabes), one finds that this difference in craniotabes frequency is statistically significant with a critical ratio value of 3.6.

When dividing the infants into three groups—77 infants with head circumference 32 cm or below, 391 infants with head circumference 33–35 cm and 91 infants with head circumference 36 cm or more—the frequency of congenital craniotabes in these three groups is 37.7 per cent, 24.3 per cent and 12.1 per cent, respectively (i.e., with increasing head circumference craniotabes frequency decreases). By such a classification the difference is significant between large heads in comparison with small heads (critical ratio value 3.94), as well as average heads (critical ratio value 3.0), while the difference between average and small heads only is suggestive (critical ratio value 2.3).

7. *Duration of foetal life*

As prematurely born infants, the author has regarded those where the duration of pregnancy has been shorter than 260 days, and as postmaturely born, those where the duration of pregnancy has been 300 days or more.

In 74 prematurely born infants congenital craniotabes was found in 20.3 ± 4.68 per cent and in 57 postmaturely born infants in 10.5 ± 4.06 per cent. The difference is statistically non-significant.

8. *Cephalhaematoma*

Reiss and Boder found cephalhaematoma in 0.9 per cent in infants with a hard skull and in 1.5 per cent in infants with congenital craniotabes. The difference was, however, statistically non-significant.

In the author's material, cephalhaematoma was found in only 8 of 559 first-born infants (i.e., in 1.43 per cent). It occurred in 1.18 per cent of

those with a hard skull and 2.22 per cent of those with congenital craniotabes. This difference was statistically non-significant. The cephalhaematomas were found to be on the same side at which the craniotabes was most marked.

9. *Maternal age*

Reiss and Boder found that infants with congenital craniotabes tend to occur more frequently among those born of older primiparae and younger multiparae.

In the author's material the mean value of the mother's age among the first-born infants with a hard skull has been 23.75 years and among the first-born infants with congenital craniotabes 23.35 years. In this study, 359 mothers were 24 years old or less (25.4 per cent of their children had congenital craniotabes), and 200 mothers 25 years old or more (22 per cent of their children had congenital craniotabes). The difference is statistically non-significant.

10. *Seasonal variation*

Several investigators reported a seasonal variation of congenital craniotabes. Boder found a direct relationship to the sunshine curve and to deficient maternal exposure to sun during pregnancy. In her study, there was a low incidence of congenital craniotabes among those born in the spring and summer.

In the author's study, there was no definite seasonal variation. The small differences observed have no statistical significance.

11. *Pelvic measurements of mother*

Among 393 primiparous with infantswith a hard skull the mean external conjugate (Baudelocque's) diameter was 19.91 cm. Among 129 primiparous mothers with infants with congenital craniotabes the mean external conjugate was almost the same (19.96 cm).

12. *Duration of labour*

Boder found no difference in the duration of labour for infants with hard or soft skulls.

Neither has the author found any such difference when he worked out the average duration of labour for 419 first-born infants with a hard skull and for 133 first-born infants with congenital craniotabes. The reliability of such a comparison is, however, questionable in this material since the duration of labour has been obtained from the mothers' uncertain and very often subjective information regarding onset.

Serum calcium, serum inorganic phosphorus and serum phosphatase

In 10 infants with congenital craniotabes, analysis of serum calcium, serum phosphorus and serum phosphatase has been made one or two days after birth, before the infant had yet begun to take any vitamin D. In

of these infants, craniotabes has been + + + and in 5 of these the parietal bone was as thin as paper. In all cases, all serum analyses have been within the normal limits indicated by v. SYDOW, the methods adopted having been identical with this author's.

In four cases, the same analyses have also been made on serum from the mother the day after the delivery, and here, too, all the values have been normal.

Roentgen examination

The right wrists of 40 infants with congenital craniotabes have been roentgenologically examined shortly after birth. Of these, 38 infants had craniotabes + + + and 2 infants craniotabes + +. During the next few months after birth, while craniotabes still remained, 25 infants were roentgenologically examined once or several times. In all, nearly 100 roentgen examinations were made. In no case have any of the roentgenological signs of rickets, as described by ELIOT, been observed.

The localisation of congenital craniotabes

HUGHES found among 76 instances with congenital craniotabes the right side affected alone in 27 and the left alone in 13.

The author has also studied the localisation of congenital craniotabes. Among 228 infants born with vertex presentation and having congenital craniotabes, this was equally marked on both sides of the skull in 61 cases, whereas, it was more marked on the right side in 103 cases (craniotabes was found only on the right side in 74 cases), and more marked on the left side in 64 cases (craniotabes was found only on the left side in 51 cases). One hundred and three cases of the 167, or 61.7 $\pm$ 3.8 per cent, had craniotabes mainly on the right side. This predilection for the right side is statistically significant.

What can be the cause of this difference? Can it be that the infant is more often lying in the uterus in a right-sided position than in a left-sided one? With *right-sided* position the author means that the face of the foetus points to the right side of the maternal pelvis (first position, LOA and LOP). With *left-sided* position the face of the foetus points to the left side of the maternal pelvis (second position, ROA and ROP).

In 1351 deliveries with vertex presentation, where the position of the infant in the mother's uterus was indicated, the infant was lying in a right-sided position in 965 cases (71.4 per cent), and in a left-sided position in 386 cases (28.6 per cent). Such a difference is well known in the literature.

In 228 infants with congenital craniotabes the position of the infant before delivery has been stated in 217 cases, and the percental division has

here been exactly the same. 155 infants (71.4 per cent) have been lying in a right-sided position and 62 infants (28.6 per cent) have been lying in a left-sided position. This difference is statistically significant.

Of the 167 cases, where congenital craniotabes was more marked on one of the sides, the intra-uterine position of the infant has been stated in 157 cases, 117 right-turned and 40 left-turned, 95 (60.5 per cent) with the craniotabes mainly on the right side, and 62 (39.5 per cent) mainly on the left side. Table 3.

TABLE 3

The localisation of congenital craniotabes in relation to different intra-uterine positions of the infants.

Intra-uterine position of the infant	Congenital craniotabes mainly on				Total
	the right side of the skull		the left side of the skull		
	Observed	*Expected*	Observed	*Expected*	
Right-sided (face turned to right side)	79	*71*	38	*46*	117
Left-sided (face turned to left side)	16	*24*	24	*16*	40
Total	95		62		157

Of these cases, the infant was lying in a left-sided position in utero and then got craniotabes on the left side in 24 cases, or it was lying in a right-sided position and then got craniotabes mainly on the right side in 79 cases. This means that in 103 cases out of 157, the infant got its craniotabes mainly on that side of the head which was turned forward while forcing its way down through the pelvis, and the other 54 cases got craniotabes mainly on the other side.

If the position of the foetus could not in any way be correlated with the localisation of craniotabes, then 60.5 per cent, or 71 of 117 right-sided infants, would have had craniotabes predominating on the right side and 39.5 per cent, or 46 craniotabes predominating on the left side. The observed figures, however, were 79 and 38 respectively, i.e., an over-representation of craniotabes predominating on the right side. In the same way, the "expected" values for left-sided would be 24 (60.5 per cent of 40) and 16 (39.5 per cent of 40) instead of the observed 16 and 24. Consequently an over-representation of craniotabes on the left side has been found. Computed

by the Chi square test the tendency mentioned above becomes highly probable; the risk of its being an accidental distribution is less than 0.01.[1]

Thus, it is that side of the foetus head which is turned forward while penetrating into the pelvis which most often gets craniotabes. Does this pressure effect occur on the foetus head when the foetus, before and during delivery, is pressing against the symphysis pubis and the anterior part of the ischio-pubic rami?

I have found no similar data in the literature to use for comparison.

Histology

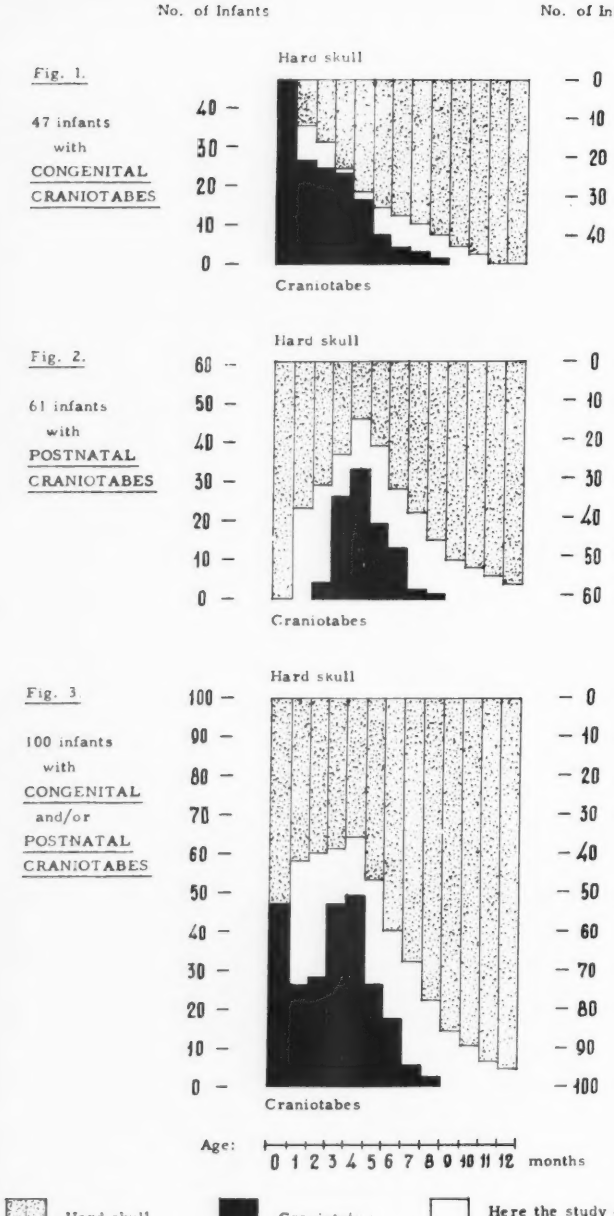
One infant with congenital craniotabes who died directly after delivery on account of lung atelectasis, has been examined histologically by Stig Ranström, M.D., Uppsala. The macroscopic examination showed the soft areas of the parietal bones to be thinner than the surrounding bone sections, and this was also verified by histological examination, which only showed an extremely thin zone of osteoid beneath the periosteum. Histologically there was no picture of rickets.

B. Congenital and Postnatal Craniotabes

Of the 1541 infants who have been examined during the investigation year in the Obstetric Wards at Sundsvall, it has been possible to follow up 274 infants (born without complications and with vertex presentation) more regularly during the first and in most cases also during the second year. These 274 infants live in the town of Sundsvall, and are regularly seen at the Child Welfare Centres of Sundsvall, which are attended to by pediatricians at the Children's Hospital in Sundsvall. In this material, breast feeding is very common, and rickets prophylaxis and health control are very good. These children have first been examined twice after the birth in the obstetric wards and then, as a rule, at intervals of one to three months during the first year, and at least once during the second year at the Child Welfare Centre.

If the child has shown craniotabes at two or more examinations following each other, it has been supposed to have had craniotabes also during the interval. If it has not had craniotabes at two or more examinations following each other, it has been supposed not to have had craniotabes during this period.

[1] For advice about and help with this statistical problem I am much obliged to Nils Fasén, M.D., Gothenburg.



Figs. 1, 2 and 3. The frequency of congenital and postnatal craniotabes at birth and during the first 12 months.

Immediately after delivery 47 infants had craniotabes, forming the "congenital craniotabes group". Among 61 infants, craniotabes appeared later during the first year, and those form the "postnatal craniotabes group". (Figs. 1, 2 and 3.)

In Fig. 2, the infants in the postnatal craniotabes group have been supposed not to have had craniotabes from birth to the last negative examination before it is observed for the first time, and in Figs. 1 and 2 the infants of the congenital as well as of the postnatal craniotabes groups have been supposed not to have had craniotabes after the examination when this had disappeared for the first time after the craniotabes period.

Through this procedure a fairly sure craniotabes-negative period has been obtained (see figures) and a fairly certain craniotabes-positive period, and in between a white area where the examination was not able to give information as to whether craniotabes existed or not, because it has not been possible, for practical reasons, to examine the infants. The white area was biggest during the first three months of life, because after the two examinations in the obstetric ward the infants have, as a rule, not been examined until the age of three or four months (an exception being the children with congenital craniotabes). Where possible, these children have been examined each month at the Child Welfare Centre until their craniotabes disappeared.

Eight cases had both congenital and postnatal craniotabes with an interval period, when, by examinations, they surely did not have craniotabes. In Fig. 1 only their "congenital craniotabes period" has been included and in Fig. 2 only their "postnatal craniotabes period". In Fig. 3, which is a mixture of the congenital as well as the postnatal craniotabes group, both craniotabes periods of these eight cases have been included.

If they had been examined often enough, possibly still more than these eight cases out of the 47 cases with congenital craniotabes should have turned out also to have had postnatal craniotabes. Likewise, several infants, who at all examinations had no craniotabes, might have shown craniotabes signs during some shorter period. In addition, it is easy to overlook the existence of milder forms of craniotabes, and probably this has happened on exceptional occasions during this investigation.

From the above it will be seen that the frequency and duration of craniotabes indicated in this study are minimum values.

Of the 274 infants examined, 136 were boys and 138, girls. Of these, 115 infants have been born of primiparae and 159 of multiparae.

Of 115 infants of primiparae 29 have had congenital craniotabes = 25.2 per cent.
Of 159 infants of multiparae 18 have had congenital craniotabes = 11.3 per cent.
Of 274 infants 47 have had congenital craniotabes ..... = *17.2 per cent.*

Of 115 infants of primiparae 21 have had postnatal craniotabes = 18.3 per cent.
Of 159 infants of multiparae 40 have had postnatal craniotabes = 25.2 per cent.
Of 274 infants 61 have had postnatal craniotabes ..... = *22.3 per cent.*

Of 274 infants 100 (50 boys and 50 girls) had craniotabes at birth or later (36.5 per cent). Eight infants had both congenital and postnatal craniotabes.

The degree of congenital craniotabes has been found to be equal on both sides of the skull in 19 cases, more marked on the right side in 17 cases and more marked on the left side in 11 cases. It has most often been localized to the vertex of the skull, but as the head has grown it has moved farther back towards the posterior parts of the parietal bones towards the place where the head rests against the bed.

The degree of postnatal craniotabes has been found to be equal on both sides of the skull in 37 cases, more marked on the right side in 12 cases, and more marked on the left side in a further 12 cases. It has most often been localized to the posterior parts of the parietal bones where these have been resting on the bed when the infant is lying. When craniotabes has disappeared, the back of the head has often been flat, or, if craniotabes was unilateral, the head was markedly asymmetrical, bearing witness to the infant's having had craniotabes. Often those infants having craniotabes predominating on one side have had a great inclination for lying on just that side, and it has happened several times that if the infant has begun instead to lie mostly on the other side, its craniotabes has also moved over to that side.

None of the 274 infants has shown any sign of rickets. In 48 cases with more marked postnatal craniotabes, 77 roentgen examinations of the right wrist have been made during the craniotabes period, but no roentgenologic signs of rickets were present in any case.

As far as it has been possible to follow the 61 infants with postnatal craniotabes, all had prophylactic vitamins in the form of 3000 units of vitamin A and 1500 units of vitamin D, daily, from the age of 7 days. Forty-seven of the infants have been breast-fed for at least 3 months, and 38 of these have been breast-fed for at least 5 months. Both slight and marked cases of craniotabes have remained for several months without being noticeably affected by the administration of vitamin D or by sunshine. The infants who, since birth, have craniotabes (the congenital craniotabes group) often have had it more marked and of longer duration than those who acquired their craniotabes postnatally.

As is seen from Fig. 3, the age of the infants in both craniotabes groups partially coincides, making it impossible to decide in the examination of an infant with craniotabes whether this is congenital or postnatal, if the

infant had not been examined at birth. Possibly the localisation might give a certain guidance. Craniotabes across the vertex speaks in favour of congenital origin, whereas craniotabes farther back on the parietal bone might be congenital as well as postnatal.

Conclusions

This study has shown that congenital craniotabes has very seldom appeared in breech presentations and in Caesarean delivery and that congenital craniotabes in twins has only appeared in the first born twin. Congenital craniotabes has been more frequent and often more marked in those born of primiparae than of multiparae.

Congenital craniotabes has been most frequent on the right side of the skull, when the infant's face in utero was turned to the right, while those who were lying in a left-sided position, usually got their craniotabes mainly on the left side. Consequently it is the side of the infant's skull, which before and during delivery is pressing against the symphysis, which most often has shown craniotabes. As it will be remembered, the first-born infant often lies with its head fixed in the pelvic entrance several weeks before partus, and during this the parietal bone, which usually later shows craniotabes, is pressing against the symphysis and the anterior part of the ischiopubic rami for a long time.

There was a predilection for infants below average birth weight, length and head circumference but there has been no certain proof that the frequency of congenital craniotabes has been affected by the infant's sex, mother's age or pelvic measurement, time of the year or the duration of delivery.

In the cases where analysis of serum phosphatase, serum phosphorus and serum calcium have been made, these values have been normal in infants and mothers and roentgen examination of the wrist in all cases examined have shown no roentgenological signs of rickets. In one case of congenital craniotabes, where the parietal bones were examined histologically, no microscopic signs of rickets were found, but only a thinning of the bone.

Thus, the investigation speaks in favour of the theory that the cause of congenital craniotabes in this material has been an intra-uterine mechanical pressure effect on the infant by the pelvic bones and the author has not in any case found any basis for a rachitic aetiology of congenital craniotabes.

In a smaller group of the material, the author has studied the frequency of both congenital and postnatal craniotabes and in 36 per cent found one

form or the other. No cases of rachitis have been found in this group. The author is of opinion that the cause of the non-rachitic postnatal craniotabes in this study also is a mechanical pressure effect on the infant's head, but in this case due to the pressure of the head in a horizontal position.

Postnatal craniotabes, however, as is well known, is often found during the first year in infants with rickets. In a special group of 35 infants, not included in this study, with roentgenologically or serologically established rickets which began before the age of eight months and who have been examined at the Children's Hospital in Sundsvall during the last six years, 22 infants also had craniotabes among other signs. In twelve of these cases craniotabes was rather marked.

The study allows the conclusion that congenital as well as postnatal craniotabes is so frequent among infants proved to be free of rickets, that one should not diagnose rickets in an infant only by the symtom of craniotabes, not even if this is very marked. One must keep in mind that each third infant at some time during its first year presents a non-rachitic craniotabes, while the real rachitic cases one finds within this period of age will probably not infrequently lack craniotabes.

Summary

The author has examined 1541 newborn infants in regard to the occurrence of congenital craniotabes. In deliveries free of complications and with cephalic presentation this sign was found in 24.2 per cent of infants born of primiparae and in 10.8 per cent of infants of multiparae. Of 100 breech-born infants only one had congenital craniotabes. Congenital craniotabes has been more often found on the right side of the head than on the left, and it has most frequently appeared on the side of the skull which, during delivery, is pressing against the symphysis. There was no difference of sex. Two hundred and seventy-four infants have been observed also during the first year. Of these, 17.2 per cent have had congenital craniotabes and 22.3 per cent postnatal craniotabes. These two forms of craniotabes show a difference in localization in so far that the postnatal type is localized farther back in the parietal bones. The author maintains that the cause of congenital as well as postnatal craniotabes in this study is a mechanical pressure on the skull, and he does not find any criterion for a rachitic aetiology. On the other hand, postnatal craniotabes may certainly also often be found in conjunction with rickets.

Craniotabès non-rachitique.

L'auteur a examiné 1541 nouveau-nés, quant à l'existence éventuelle d'un craniotabès. Dans les naissances exemptes de toute complication, avec présentation céphalique, le craniotabès a été décelé chez 24,2 % des enfants nés de primipares et 10,8 % des enfants de multipares. Sur 100 présentations du siège un cas seulement de craniotabès fut observé. Le craniotabès congénital a été observé plus souvent sur le côté droit de la tête que sur le gauche et le plus souvent sur le côté du crâne qui appuyait sur la symphyse pendant la délivrance. On n'a relevé aucune différence en rapport avec

le sexe. 270 enfants ont également été suivis au cours de la première année. 17,2 % de ceux-ci avaient un craniotabès congénital et 22,3 % un craniotabès acquis après la naissance. Ces deux formes de craniotabès montrent une différence de localisation: le type acquis se localise plus en arrière sur les pariétaux. L'auteur affirme que, dans cette étude, la cause du craniotabès aussi bien acquis que congénital réside dans une pression sur le crâne et ne relèvent aucune étiologie rachitique. D'autre part, le craniotabès acquis peut certainement être trouvé aussi souvent en association avec le rachitisme.

Nichtrachitische Craniotabes.

Der Verf. hat 1541 Neugeborene mit Hinblick auf das Auftreten von kongenitaler Craniotabes untersucht. Bei komplikationsloser Entbindung und Kopflage wurde diese Erscheinung in 24,2 % der Kinder von Primaparae und in 10,8 % der Kinder von Multiparae beobachtet. Von 100 in Steisslage geborenen Kindern hatte nur eines kongenitale Craniotabes. Kongenitale Craniotabes ist öfters auf der rechten Kopfseite als auf der linken gefunden worden und trat am häufigsten an der Seite des Schädels auf, welcher während der Entbindung gegen die Symphyse drückt. Geschlechtlich trat kein Unterschied auf. 270 Kinder sind ebenfalls während des ersten Lebensjahres beobachtet worden. 17,2 % von diesen haben kongenitale Craniotabes gehabt, und 22,3 % postnatale Craniotabes. Diese zwei Formen der Craniotabes zeigen unterschiedliche Lokalisation insofern als der postnatale Typ weiter rückwärts in den parietalen Knochen lokalisiert ist. Der Verf. behauptet, dass die Ursache sowohl der kongenitalen als auch der postnatalen Craniotabes in dieser Untersuchung einen mechanischen Druck auf den Schädel darstellt, und er findet kein Kriterium für eine rachitische Ätiologie. Auf der anderen Seite kann doch postnatale Craniotabes sicherlich auch oft im Zusammenhang mit Rachitis gefunden werden.

Craneotabes no raquítico.

El autor ha examinado 1541 recién nacidos con el fin de determinar la presencia de craneotabes. En partos sin complicaciones y con presentación cefálica se encontró en 24,2 % de los hijos de primíparas y en 10,8 % de multíparas. En 100 niños nacidos con presentación podálica solamente uno tenía craniotabes congénito. El craniotabes congénito se le ha encontrado más amenudo en el lado derecho de la cabeza que el izquierdo. Y se ha visto que es más frecuente en el lado del cráneo que, durante el parto, se apoya sobre la sínfisis púbica. No se hallaron diferencias en relación al sexo. 270 niños fueron observados también durante el primer año: 17,2 % habían tenido craneotabes congénito, y 22,3 % postnatal. Estas dos formas de craniotabes muestran diferencias en localización de tal manera que el postnatal está localizado más hacia atrás en los huesos parietales. El autor sostiene que la causa del congénito, así como del craneotabes adquirido es debido a la presión sobre el cráneo, no habiendo encontrado ningun indicio favorable a una etiologia raquítica. Por otro lado el craniotabes postnatal fué amenudo encontrado en conjunción con raquitismo.

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Received Sept. 15, 1954

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Acta Pædiatrica **44**: 203—208. May. 1955

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Three Months' Colic

Treatment by Methylscopolamine Nitrate ("Skopyl")

by R. S. ILLINGWORTH

The term "three months' colic" is reserved for those babies who, in the first three months of their life, are otherwise well and receiving all the food they want, but who have severe spasmodic attacks of abdominal pain in the evenings. Their crying does not stop when they are picked up and cuddled. I have recently reviewed the whole subject (ILLINGWORTH, 1954) and emphasised the ease with which an incorrect diagnosis can be made. It was suggested that the most likely explanation of the attacks was local obstruction to the passage of gas in the bowel by spasm or other cause.

NYMAN (1943, 1944) described a new antispasmodic anticholinergic drug, methylscopolamine nitrate ("skopyl"), and claimed that it was much more effective than atropine sulphate or methylatropine nitrate ("eumydrine"). The drug has been used successfully for the relief of gastric ulcer pain, and for biliary and renal colic. JORUP (1952) achieved excellent results with the use of "skopyl" for "three months' colic" (termed by him "colonic hyperperistalsis in neurolabile infants").

For the past eighteen months a controlled investigation into the use of skopyl for three months' colic has been in progress at the Jessop Hospital for Women at Sheffield, and this paper presents an analysis of the results.

Material and Methods

The material consisted of 40 consecutive babies with moderate or severe three months' colic. Mild cases were excluded. All babies were seen by me personally. All babies satisfied the rigid criteria for diagnosis previously laid down (ILLINGWORTH, 1954). They all had rhythmical screaming attacks in the evenings (repeated attacks of screaming, lasting a few minutes, with quiet spells in between): in no case did the crying stop when the baby was picked up: in all cases the weight gain was 6 ounces or more per week during the period of investigation (average gain 8.7 ounces per week): in all cases the colic started in the first month of life (in many cases in hospital), and in all cases it stopped by the time the baby was three months old. In no case was there any other discoverable cause for the rhythmical screaming attacks,

and all the babies were otherwise well and thriving, no abnormal physical signs being found on examination.

When a baby satisfied the above criteria for admission to the investigation, "skopyl" was prescribed in the dosage recommended by the makers—1 drop (0.05 mg skopyl per drop) four times a day sublingually before feeds, one of these feeds being that given at about 6.00 p.m., before the colic was expected to begin. On receiving the prescription card the Chief Pharmacist, Miss C. WOOD, dispensed either skopyl or a control substance (a weak solution of ascorbic acid) allocating the cases by random sampling, and made the appropriate record in a book which she kept. In all cases I saw the mother and baby one week later and at intervals subsequently, recording the exact words used by her when she was asked how the colic had responded to the treatment. In 5 cases, when the response had been unsatisfactory, the dose was increased to 5 or 6 drops per day, two drops being given before the 6.00 p.m. feed. (One of these cases proved to be a "control".) The average duration of treatment was 17.9 days.

When 40 babies had been treated, a table was drawn up, containing the relevant data, including the exact words used by the mother in describing the effect of the drug. The remarks were then converted into a "score" for the purposes of analysis. If a baby was said to be completely cured by the drops, with no further screaming at all, the score was recorded as +4. If he was said to be a great deal better, but still having screaming attacks, though much less severe, he was given a score of +3. If the drops made him worse, he was given a score of −1 to −4, according to the words used by the mother. For the purpose of tabulation in this paper babies given a score of +1 or +2 were considered to be "Better"; those given +3 or +4 to be "Much better"; those given −1 or −2 to be "Worse"; those given −3 or −4 to be "Much worse". *Only when the grading had been completed did I obtain the code from the Chief Pharmacist, stating whether the patient had had "skopyl" or the control substance.* The groups were then analysed separately for comparability and for the results.

Comparability of the Two Groups

Table 1 shows the relevant data. It will be seen that there is no significant difference between the two groups. The mean age at which treatment began was $4^1/_2$ weeks in each group: babies in the skopyl group weighed on an average $5^1/_2$ ounces above the expected weight on admission to the investigation, as compared with 9 ounces in the control group. The mean weekly weight gain during the investigation was 9.4 ounces in the skopyl group and 8.2 ounces in the control group. Sixteen babies in each group were fully breast fed.

Results

Table 2 shows the results. It will be seen that 5 babies in the skopyl group were "much better or cured" when given the drops, as compared with 9 in the control group. Nine babies in the skopyl group and 7 in the con- trol group were "better". One child in the skopyl group was made

TABLE 1

Comparability data.

20 babies in each group.

	Treated	Controls
First born	13	12
Female	7	11
Full term	16	20
Birth weight (Mean, lbs. & ozs.)	7.1	7.7
Standard Error	0.5	0.3
Number fully breast fed during the investigation	16	16
Mean weight in ozs. at time of starting treatment in relation to expected weight[1]	+5.5	+9.0
Standard Error	2.1	2.6
Mean weight gain in ozs. per week during the investigation	9.4	8.2
Standard Error	0.7	0.5
Age at which treatment began (wks.)	4.5	4.5
Standard Error	0.4	0.3
Approximate duration of treatment (Mean, days)	17.3	18.5
Standard Error	1.9	1.8

[1] The expected weight was calculated by allowing 1 oz. weight gain per day from birth, and deducting 10. +5 means 5 ounces above the expected weight.

TABLE 2

Results of treatment.

20 babies in each group.

	Skopyl Group	Control Group
Much better or cured	5	9
Better	9	7
No change	1	4
Worse	1	0
Much worse	4	0

worse, and 4 babies in the same group were made "much worse". The "score" achieved by the 20 babies in the skopyl group was +12 (+29—17) as compared with +38 in the control group.

The actual words used by the mothers of the babies who were classified as "much worse" (skopyl group) were as follows:

(i) "He was much worse, so I stopped the drops after 2 nights."

(ii) "He was much worse, so I stopped the drops after 3 days."

(iii) "He has had a terrible week. He is worse than ever. The screaming is shocking."

(iv) "The drops which you advised for her have almost sent her into a fit each time, so I stopped giving them to her. She was terrible."

The words used by some of the mothers whose babies had been given control drops were as follows:

(i) "He's been fine. He's been right contented since you gave him the drops. He's been no trouble at all."

(ii) "The crying is nothing to what it was before. The drops definitely helped him. The yelling in the evenings has stopped."

(iii) "There's been a big difference. He's only had two restless evenings, and then he settled when we played with him. The drops definitely helped."

(iv) "The drops certainly helped him. He's been a lot better in the evenings."

(v) "He hasn't had a single attack after you gave him the drops until last night. Before that he had them every night."

It is interesting to note that none of the babies were completely relieved of their screaming attacks ("cured") by the control drops: the skopyl "cured" one baby.

The conclusion was reached that skopyl in the dose used was of no value.

Discussion

In a self-limiting condition, or one in which spontaneous remissions are common, it is easy to give a drug credit for curing a patient when in fact it has achieved nothing. Furthermore, there is a widespread popular belief in the magic of medicine, and only a carefully controlled study can be expected to provide a satisfactory answer to the question of whether the drug is of value or not. In such a study, of course, it is essential to ensure, firstly, that the diagnosis is correct, and secondly that the drug is active, and is given in proper dosage. The skopyl used in this investigation was supplied in 5 cc bottles so that bottles would not be left open long enough to deteriorate. The makers stated that no deterioration would occur in the closed bottles. As for the dosage, this was in accordance with that recommended by the makers and it was increased in 4 babies. Atropine derivatives have to be given to babies with care in an out-patient department, because of the danger of toxic reactions, and it was felt that it would be unsafe to increase the dose further.

Three months' colic is a self-limiting disorder, in that it disappears spontaneously by the time the baby is 8 to 12 weeks or so of age, and no doubt this fact largely explains the "success" of the control drops in alleviating the symptoms.

The conclusion was reached that 'skopyl', used in the dosage described, was not of value in treatment of three months' colic.

Summary

1) In a controlled investigation of 40 babies with three months' colic, using rigid criteria for diagnosis, 20 babies were given skopyl (methylscopolamine nitrate), and 20 were given a control substance. The babies were seen at intervals and the exact words used by the mothers to describe the effect of treatment were recorded. Only when their responses had been analysed and graded was it determined whether the babies had been given skopyl or a control substance.

2) Five babies in the skopyl group and 9 in the control group were thought to be much better as a result of treatment. Nine babies in the skopyl group and 7 in the control group were "better". Five babies in the skopyl group were thought to be worse as a result of treatment (4 much worse), as compared with none in the control group.

3) The conclusion was reached that skopyl, as used in this investigation, was of no value in treatment.

Traitement par le nitrate de méthylscopolamine (Skopyl).

Au cours d'une étude contrôlée de 40 nourrissons atteints de «colique de 3 mois» soumis à de sévères critères de diagnostic, 20 de ces sujets reçurent «Skopyl» (nitrate de méthylscopolamine) et 20 une substance de contrôle. Les enfants furent revus régulièrement et les mots mêmes employés par la mère pour décrire l'effet du traitement furent notés. Ce n'est que quand leurs réponses eurent été analysées et cotées que l'on vérifia si les enfants avaient reçu Skopyl ou la substance témoin. 5 enfants dans le groupe Skopyl et 9 dans le groupe témoin furent considérés comme très améliorés. 9 enfants dans le groupe Skopyl et 7 dans le groupe témoin furent trouvés «mieux», 5 sujets du groupe Skopyl furent jugés plus mal après le traitement (4 beaucoup plus mal) contre aucun dans le groupe témoin.

Behandlung mit Methylscopolamine Nitrate („Skopyl").

In einer kontrollierten Untersuchung von 40 Säuglingen mit 3monatlicher Kolik, wobei strenge diagnostische Kriterien verwandt wurden, erhielten 20 Säuglinge Skopyl (Methylscopolamine Nitrate) und 20 anderen wurde eine Kontrollsubstanz verabreicht. Die Säuglinge wurden in Zwischenräumen observiert und die exakten Worte, mit denen die Mutter den Behandlungseffekt beschreibt, aufgezeichnet. Erst als die Antworten analysiert und eingeteilt worden waren, wurde festgestellt, ob dem Säugling Skopyl oder Kontrollsubstanz verabreicht worden war. Fünf Säuglinge der Skopyl-Gruppe und neun in der Kontrollgruppe wurden als durch den Behandlungseffekt stark verbessert angesehen. Neun Säuglinge der Skopyl-Gruppe und sieben in der Kontrollgruppe waren verbessert. Fünf Säuglinge der Skopyl-Gruppe wurden als

durch die Behandlung verschlechtert bezeichnet (vier davon viel schlechter), gegenüber keinem in der Kontrollgruppe.

Tratamiento por nitrato de metilescopolamina ("Skopyl").

En una investigación controlada de 40 niños con «cólicos de tres meses», usando un criterio diagnóstico rígido, se le administró la mencionada sustancia a un grupo de 20 niños, mientras que a otro grupo de 20 se le administró una sustancia control. Los bebés fueron vistos a intervalos y se anotaron las palabras exactas de la madre al describir el efecto del tratamiento. Sólo después de haber analizado y clasificado las palabras maternas se determinó si al niño se le había administrado skopyl o la sustancia control. Cinco niños del grupo que se le administró skopyl y nueve del grupo control se supusó que estaban mucho mejor como resultado del tratamiento. Nueve del grupo skopyl y siete del control estaban «mejor». Cinco niños del grupo skopyl se encontraron peor (cuatro mucho peor), mientras que ninguno del grupo control se consideró empeorado.

Acknowledgments

My thanks are due to A.B. Pharmacia of Uppsala, for so kindly supplying the drug for the experiment, and for their advice about dosage. My particular thanks are due to Miss C. Wood, M.P.S., Chief Pharmacist at the Jessop Hospital, for her willing co-operation and for her careful records. My thanks are due to Miss W. M. Gibson, B.A., of the Department of Mathematics in the University, for the calculation of standard errors.

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Received Nov. 30, 1954

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Acta Pædiatrica **44**: 209—218. May 1955

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Nephrogenic Diabetes Insipidus in Children

by ÅKE ELLBORG and HANS FORSSMAN

WARING, KAJDI and TAPPAN (1945) described a disorder in water metabolism in six children, all males. The syndrome, manifested shortly after birth, was characterized by polyuria and polydipsia, erratic and unexplained fever, persistent constipation, and vomiting. The excessive thirst and urination did not respond to pituitrin. Three of the six boys were half-brothers. However, it was not stated whether they had the same mother or father and the heredity of the children is not discussed in any detail.

The same syndrome was observed in boys by YUN-CHEN KAO and STEINER (1953) and MACDONALD (1953).

In 1942 and 1945 one of us (H. F.) reported a family showing a recessive, sex-linked form of diabetes insipidus of a kind not susceptible to pituitrin. (However, as was pointed out, the latter is not always true of diabetes insipidus inherited in this manner.) The same observation was later made independently by WILLIAMS and HENRY (1947). They called the disorder nephrogenic diabetes insipidus, a term which has now been adopted and will be used hereafter by the present authors. In the same article, WILLIAMS and HENRY described a boy who at the age of 2 months stopped gaining weight, became fretful, and varied a great deal in his desire for milk and water. Inexplicable fever was also present. He was thoroughly examined in a hospital at the age of six months but many studies failed to explain the child's illness. He continued to be febrile throughout the forty-five days of his hospitalization in spite of intensive treatment with antibiotics. When he was about 8 months old the diagnosis of diabetes insipidus was made. When he was a year old he weighed 6 kg and at 17 months of age 7.5 kg.

In 1953, GUARD reported the occurrence of the same disorder in two brothers. One of them died at 6 months of age of "dehydration and electrolyte imbalance"; the diagnosis of "abnormal urinary concentration power" was made. The other brother, examined at the age of 5 years, was found to have an I.Q. of 73. However, it must be noted that the examination was made about a month after a skull fracture.

Finally, one of us (H. F.) published, in 1954, further cases of sex-linked diabetes insipidus of a nephrogenic type. In this article, and the one from 1945, two male infants with a syndrome like that described by WARING and his co-workers, are reported.

In all probability all the foregoing publications have to do with the same genotypic disorder. During the past fifteen years we have come into contact with a considerable number of cases of nephrogenic diabetes insipidus in children, considering the little that has been written on the subject. Through the courtesy of other pediatric departments we have been able to follow several of the children from the time they were infants. Furthermore, study of the history of a family in which nephrogenic diabetes insipidus is hereditary revealed that three boys had died in infancy from obscure causes. These boys were so situated in the family tree that there was a fifty-fifty chance of their being afflicted. Since the disorder is rare and since it seems to involve a serious risk in infants, we now present our cases. We shall also discuss the possibility of preventing some of its most serious consequences, providing its presence is recognized in good time.

Five of our cases come from one family (Fig. 1), two come from another (Fig. 2) and the eighth is a sporadic case.

Case Reports

We shall first describe the five unequivocal cases and then the three hypothetical ones from the first family (Fig. 1).

III:13, born in 1896, died when he was 2 1/2 years old. He is mentioned in the hospital record of 1897 of III:5: "The youngest child, who is one year old, also drinks a great deal." The sister III:8 who tended him before he died is certain that he had the family's "thirst disease".

IV:7, born in 1914, died when he was 1 1/2 years old. According to his mother, the boy was always thirsty. He cried a great deal and the only way to quieten him was to give him water. He passed large quantities of urine. He became taller but grew extremely thin. He suffered from bouts of fever and vomited frequently. A physician was consulted who prescribed rationing the amount of water given to the child. This proved to be unfeasible. The mother, who had three other children, one with diabetes insipidus and two without, is quite sure that this boy suffered from the disorder.

IV:8 was born in 1921, at full term, weighing 3,750 g. Delivery was normal. He was breast-fed for four months. When he was three months old he had a "severe intestinal disorder" and his weight fell to 2,150 g. Afterwards, the mother said the child was always delicate and lagged behind in development. He learned to walk at the age of 2 years but to talk in normal time. The mother noted when he was small that, like his elder brother, he craved fluids, and so, in order to try to prevent him meeting the same fate, it was decided to let him drink as much as he wanted.

When he was 9 1/2 years old he was admitted to a pediatric department. He was described as pale and thin, but otherwise no essential signs of disease were noted.

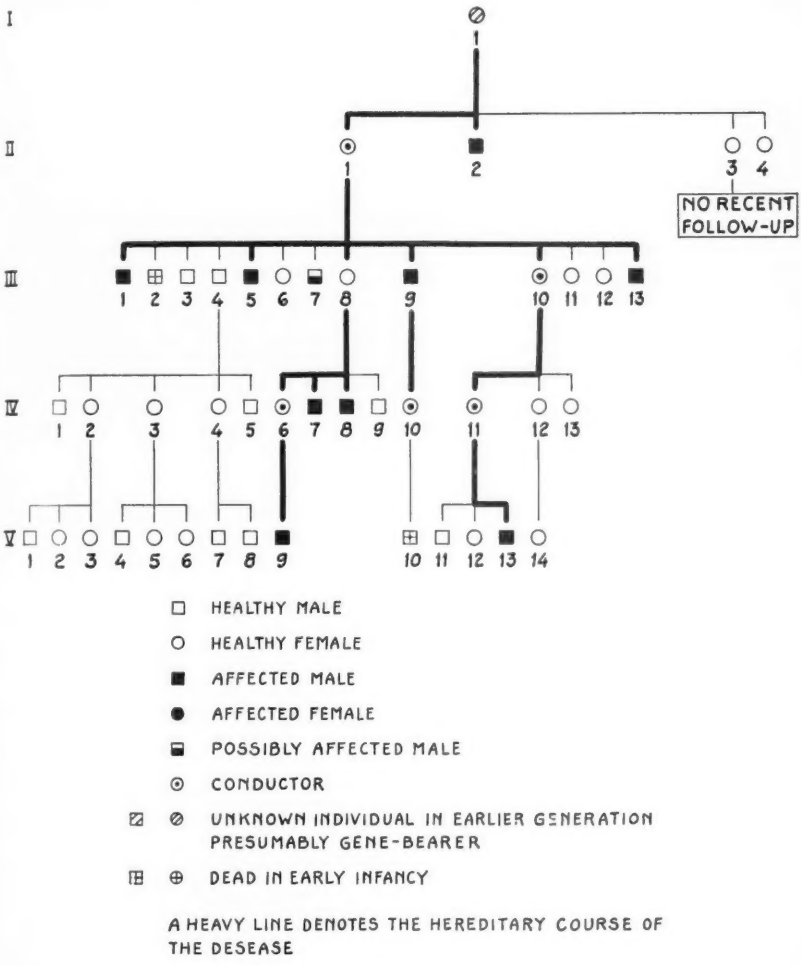

Fig. 1.

He was tested on several occasions with posterior pituitary preparations but showed no reaction. When his fluid intake was decreased, he became extremely thirsty, vomited and felt ill generally.

He followed the normal curriculum at school but as an adult he gives the impression of being dull, though not definitely below normal in intelligence.

No information is forthcoming regarding fever or constipation at infant age, either in the hospital records of 1930 or from a supplementary interview with the mother in 1954.

IV 9 was born in 1941, weighing 3,200 g. Delivery was normal. When he was six

weeks old he began to vomit a great deal and to suffer from constipation. His excessive thirst became apparent before he reached the age of one. When he was one year old he weighed 6 kg; when he was 2 years and 4 months old, he weighed 7 kg. At the latter age he was admitted to a pediatric ward because of malnutrition. Examination revealed a small and emaciated child with lowered turgor. He could only speak a few words. He could sit up by himself, but needed support to be able to walk and stand. His temperature varied a great deal, and often rose to about 40° C though no infection was present.

The presence of diabetes insipidus was already obvious at his first visit to the hospital. At the age of 13 years he was admitted to another pediatric department. There he proved to be unresponsive to the antidiuretic hormone. His Terman-Merrill I.Q. was 69. He is now in an institution for feeble-minded.

V:13 was born in 1944, at full term, weighing 4,750 g. Delivery was normal. At the age of 2 months, fever of unknown origin began, together with constipation and frequent vomiting. At the end of his third month the child weighed 4,800 g. When he was 4 months old he was admitted to a pediatric department because of fever and malnutrition; reduced turgor, depression of the anterior fontanel and dry skin were observed. The temperature varied greatly, and during the next few months it often rose to 40° C.

It was not fully certain whether diabetes insipidus was present when he first came to the hospital, but when he reached the age of one, there was no longer any question about the diagnosis. At the age of 10 years, he was tested with the antidiuretic hormone and proved to be entirely resistant. He was obviously mentally defective and had great difficulty keeping up at school. His Terman-Merrill I.Q. was 66 at 10 years of age.

Now follow the hypothetical cases from the same family:

III:2, born in 1874, died at the age of one month from an unknown disease according to the parish books.

III:7, born in 1883, died when he was $1^1/_2$ years old. According to the parish records, he had been "delicate since birth". In the 1897 hospital record of III:5, it is noted that he had a strong craving for fluid. The brother, III:9, said that he was supposed to have had the "thirst disease" but the sister, III:8, could not say anything about this.

V:10, born June 22, 1951, died when he was 4 months old. Delivery was three weeks premature but otherwise normal. He was admitted to a pediatric department when he was 2 months old for severe vomiting and fever. His mother did not mention the hereditary disorder in her family. Examination revealed reduced turgor and signs of dehydration. During his two months in the hospital he had several bouts of high fever and vomited incessantly. Despite this he ate well and increased in weight at first. Seven weeks after admission, however, his general condition deteriorated and he became apathetic and pale. The cerebrospinal fluid was normal. On October 9, he died. Autopsy was performed and signs of acute diffuse bronchitis and serous meningitis were recorded, but in the opinion of the head pediatrician they were not a satisfactory explanation for the death of the child.

We shall not take up the rest of the afflicted subjects in the family shown in Fig. 1, for they were only examined at adult age. Cases III:1, III:5 and

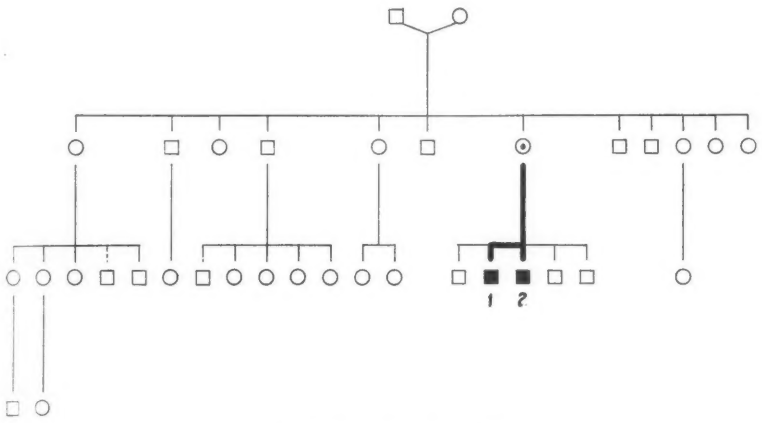

Fig. 2. Symbols as in Fig. 1.

III:9 are clinically verified. III:9 was tested with the antidiuretic hormone and proved to be unresponsive. All three, moreover, are decidedly below normal in intelligence. As for II:2, it is clear from the 1897 hospital record of III:5 that he had the disorder, but nothing definite is known about his mental capacity. Further particulars of these cases are given in the previously mentioned reports of one of us (H. F.) published in 1945 and 1954.

The following are the two cases from the second family (Fig. 2).

Case 1. This boy was born in 1943, at full term, weighing 4,200 g. Delivery was normal. Despite the fact that the disease was unknown in the family, the mother noticed before the child was six months old that he had an excessive craving for fluids. He was breast-fed until the age of 4 months. When he was changed to bottle feeding he began to vomit a great deal. Against a physician's orders, the mother let him drink as much water as he wanted after she noticed that it was the only way to keep him from becoming extremely restless. She did not notice that he had any particular tendency to fever as an infant, but he was usually constipated. His psychomotor development was normal, except for talking. When he was one year old he could say a few words, but then he made no more progress until he was 4 years old. At the age of 6 years, he was admitted to a hospital, where it was seen at once that he had diabetes insipidus. He was described as a thin and pale child, shorter than other boys of his age. Testing with the antidiuretic hormone, in doses up to 40 units each of oxytocin and vasopressin, showed him to be completely unresponsive. Apart from dilution of the contrast agent, urographic studies gave normal results.

At the age of 11, he was examined again, both at a hospital and by us at home. He was still slightly below normal in height and weight, but his general condition was good. He had developed normally mentally, his Terman-Merrill I.Q. being 99.

Case 2. This boy was born in 1944, at full term, weighing 3,700 g. Delivery was normal. He was breast-fed until he was over one year old but he was given extra water from the time he was tiny, for the mother noted that he, too, was always thirsty.

When he was small he often vomited. He was constipated until he was about 2 years old. His mother did not notice that he had any particular tendency to fever as an infant. He was duller and more listless than his elder brother. He sat up at the age of 6 months and walked at 15 months. He, too, could only say a few words before he was 4 years old.

When he was 5 years old he was admitted to a hospital. There it was realized at once that he had diabetes insipidus. He was described as pale and thin like his brother, but in addition he appeared apathetic. He was 103 cm tall and weighed 14 kg. A posterior pituitary preparation failed to elicit any response, even in doses of 40 units each of vasopressin and oxytocin a day—an extremely large dose for a child that size. Urographic examination showed nothing except dilution of the contrast agent.

At the age of 10 he was again examined, both at a hospital and by us at home. He was still small and thin. He gave the impression of being feeble-minded and our opinion was corroborated by his teacher. His Terman-Merrill I.Q. was 75.

Finally, we have the sporadic case:

No other instances of diabetes insipidus are known of in the family of this child. He was born in 1948, at full term, weighing 3,220 g. Delivery was normal. He was first examined at a hospital at the age of 2 months and during his first two years he was hospitalized altogether five months for intermittent high fever, with peaks to 40° C, vomiting and constipation. He had a number of catarrhal infections but even when there were no signs of infection the fever persisted for months. He caused a great deal of diagnostic discussion, but no explanation was found. When he was a year old he weighed 7,500 g, when he was 2 years old he weighed 8,980 g. His psychomotor development was also delayed. The case continued to be a mystery.

When he was 6 years old he again came under medical observation and this time his mother said that she had noticed for a long time that he suffered from an excessive thirst. It was then obvious that he had diabetes insipidus. Urinary outputs up to 2,700 cc per day were noted and the child exhibited an enormous craving for fluid, even drinking the water out of vases. He was tested on several occasions with the antidiuretic hormone and each time proved to be unresponsive. His Terman-Merrill I.Q. was 67, a figure which tallied with the general impression he gave, in the opinion of a child psychiatrist. Intravenous urographic examination showed slight dilatation of the renal pelvis and ureters on both sides and dilution of the contrast medium.

Comment

We have observed a syndrome in six clinically verified cases of nephrogenic diabetes insipidus which tallies well with the clinical picture first described by WARING, KAJDI and TAPPAN (1945). In addition, we have information about two other patients who obviously had the same disorder but who died young without having undergone clinical examination. Finally, we have three cases in which the diagnosis is hypothetical, but in which the genetic conditions were such that the subjects ran a 50 per cent risk of getting the disorder. These three subjects died in infancy.

The most prominent feature of the syndrome is naturally the disorder in

water metabolism. It differs from the more common and benign, hormonally conditioned form of diabetes insipidus in that it incurs a large risk of dehydration and other conditions which are probably secondary. The dehydration is manifested in the ordinary way with reduced turgor, depression of the fontanels and dry mucous membranes. However, the degree of dehydration may vary rapidly and sometimes the child will show no sign of this nature. To make sure that the condition is detected, therefore, attention must also be paid to the secondary symptoms: the intermittent, often high fever with no infection to explain it, the tendency to vomit and the constipation. The child usually stops gaining or even loses weight, and remains smaller and thinner than his contemporaries for many years. As a rule he also lags behind in mental development.

Two of our surviving children grew extremely poorly at one stage and one of them was once thought to be dying. In two of the proven cases, the patient died in infancy. Turning to the literature, we find that one of the children reported by WARING *et al.* died (although it is not said what caused the death) and one of GUARD's patients died at the age of 6 months, apparently from the disorder in water metabolism. Several of the boys in our series proved to be mentally defective after the severe nutritional disorder had subsided. We are of the impression that the cases in which the intoxication was of a mild degree in infancy, and in which the boy turned out to be relatively well-equipped mentally, were the ones in which the mother gave him plenty of fluids from the time he was tiny (IV:8, Fig. 1 and Case 1, Fig. 2).

For the child to receive proper care, the most important thing is to recognize the condition early. It is extremely difficult to make the diagnosis early in sporadic cases; this is evident both from the literature and our own experience. When the disorder is familial, a great deal depends upon whether the mother mentions the occurrence of the disorder in the family and the physician interprets the information correctly. It is seen both from WILLIAM's and HENRY's experience and our own that familial occurrence does not always lead to the disorder being recognized as early as one would desire.

Seeing that it is impossible in these cases to reduce the great loss of fluid in the urine, the only form of treatment is to give copious amounts of fluids. However, this is perhaps an efficient form of treatment, and we believe that it can spare the child the severe intoxication and dehydration which so often occur. Moreover, it may also prevent the most serious complication of all in the long run, mental inferiority, for we are inclined to believe that the mental defect we observed in most of our cases was the result of dehydration of the brain. It may be noted that subject V:9 still had fever at

the age of 2 years and 9 months. He is now one of the most retarded mentally and has been sent to an institution for feeble-minded. Our sporadic subject also still had fever at the age of 2 years and he, too, is one of the most retarded mentally.

However, once the diagnosis is made, the physician has not only to see that the child gets plenty of fluid at once. He has also to protect the child from misguided attempts to cut down the amount he drinks, for it is usually thought among laymen that his constant drinking is only a bad habit he has acquired. The family should be taught that the child needs large amounts of fluid. Arrangements should be made early to have a supply of fluid near the child's bed so that his mother can get her night's rest. Later on, when he begins school, the teacher should be told that his craving for water is due to a disease. In nearly all our cases of school children the teacher has attempted with varying degrees of mental pressure to rid the child of his "bad habit".

Summary

The authors describe eight cases of nephrogenic diabetes insipidus in children, six of them studied at a hospital. Five of the cases came from four generations of a family showing a pattern typical of sex-linked inheritance, two are brothers from another family, and the eighth is a sporadic case. These children usually showed signs of severe dehydration during the first three years of life, suffering from fever, malnutrition, and retarded physical and mental development. In two of the unequivocal cases the boys died in early childhood. There are also three boys in the large family who died in infancy from an obscure cause, and who were so situated in the family tree that there was a 50 per cent risk of their getting the disorder.

The authors emphasize the importance of an early diagnosis of this sometimes very puzzling condition, because it seems to be necessary for a favorable outcome that the child be given plenty of fluid. It is suggested that a sufficient supply of fluid in the beginning may prevent the mental deficiency often present in these cases, for the deficiency is thought to be due to dehydration of the brain. The pediatrician should also impress upon the persons in charge of the boy that his incessant drinking is not a bad habit but something he must do in order to keep well.

Diabète Insipide d'origine rénale, chez les enfants.

Huit cas de diabète insipide d'origine rénale chez des enfants sont rapportés. Cinq de ces cas appartenaient à 4 générations d'une même famille dans laquelle le diabète insipide est transmis par la voie gynécophorique; deux étaient des frères dans une autre famille et le huitième était un cas sporadique. Ces enfants présentaient habituellement des signes de déshydratation sévère au cours des trois premières années avec fièvre, malnutrition et retard du développement physique et mental. Dans 2 des cas certains les garçons moururent dans la première enfance. Dans la famille atteinte, il y eut aussi trois garçons qui moururent enfants d'une cause obscure et qui se trouvaient à une place de l'arbre généalogique telle qu'ils avaient 50 % de risques d'être

attents de la maladie. Les auteurs insistent sur l'importance d'un diagnostic précoce de cette affection complexe, car il semble nécessaire que l'enfant reçoive beaucoup de l'eau pour évoluer favorablement. A leur avis, un apport suffisant de liquide dès le début peut empêcher la rétardation mental qui se développe souvent dans ces cas; ils pensent en effet que ce déficit peut être dû à une déshydratation cérébrale. Le pédiâtre pourrait ainsi avertir les personnes qui s'occupent de l'enfant que cet apparent excès de boisson est nécessaire à sa santé.

Der nephrogene Diabetes insipidus bei Kindern.

Acht Fälle von nephrogenem Diabetes insipidus bei Kindern sind beschrieben. Fünf der Fälle stammen von vier Generationen einer Familie, welche ein typisches Beispiel von geschlechtsgebundener Erblichkeit zeigt, zwei Fälle sind Brüder einer anderen Familie und der achte ist ein sporadischer Fall. Diese Kinder zeigen gewöhnlich während der ersten drei Lebensjahre Symptome einer schweren Dehydration — Fieber, ungenügende Nutrition und verspätete physische und psychische Entwicklung. In zwei der unzweifelhaften Fälle starb der Knabe in frühem Kindesalter. Ebenfalls starben drei Knaben der grossen Familie im Kindesalter aus unklaren Gründen. Diese waren so im Stammbaum placiert, dass sie ein 50%iges Risiko des Krankheitsausbruches liefen. Die Verff. betonen die Wichtigkeit der Frühdiagnose bei diesem manchmal rätselhaften Verhältnis, da es für eine günstige Entwicklung notwendig erscheint, dass das Kind reichlich Flüssigkeit erhält. Ihrer Meinung nach kann eine genügende Zufuhr von Flüssigkeit zu Beginn der Krankheit dem psychischen Defizit, das oft in diesen Fällen vorkommt, vorbeugen, da sie glauben das Defizit einer Gehirn-Dehydration zuschreiben zu dürfen. Der Pädiater muss ebenfalls die Pflegeperson des Kindes darauf aufmerksam machen, dass sein unaufhörliches Trinken keine schlechte Angewohnheit ist, sondern eine Reaktion des Kindes darstellt, das Wohlbefinden aufrechtzuerhalten.

Diabetes insípida nefrogénica en niños.

Se describen 8 casos de diabétes insípida nefrogénica en niños. Cinco de ellos, provenientes de cuatro generaciones de una misma familia, muestran una clara herencia ginecofórica, otros dos son hermanos de otra familia y el octavo es un caso esporádico. Estos niños mostraron, durante los primeros años de la vida, signos de seria deshidratación fiebre, desnutrición y retraso físico y mental. Dos casos inequívocos fallecieron en la primera infancia. En esta misma familia fallecieron además de causa indeterminada 3 niños situados de tal modo en el árbol genealógico que su riesgo de padecer la affección era del 50 %. Los autores destacan la importancia de un diagnóstico precoz ya que para una evolución favorable de esta afección es necesaria la administración de una gra cantidad de líquidos. Sugieren además que un adecuado aporte fluido desde el comienzo pueda prevenir el déficit mental, que a menudo presentan estos pacientes, y que podría deberse a los efectos de la deshidratación sobre el sistema nervioso central. El pediatra debe instruir a las personas a cargo del niño en sentido de no combatir su continua necesidad de beber, lo cual lejos de ser un mal hábito es una necesidad.

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Received Nov. 30, 1954

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Acta Pædiatrica **44**: 219—236. May 1955

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Fatal Tuberculosis from BCG Vaccination

by STURE FALKMER[1], ARNE LIND[2] *and* LENNART PLOMAN

During the last decades BCG vaccination as a prophylaxis against tuberculosis has been used on an increasingly large scale. More than 60 million persons have been immunized in this way (IRVINE, 1954). The intradermal mode of vaccine application, introduced by WALLGREN, 1927, is nowadays the most widely adopted method. Until recently no serious complications had been reported from the vaccination. They consisted mainly of local abscesses and regional adenites, sometimes with suppuration. These effects are encountered especially in infants. Some rare cases are reported of local tuberculous skin lesions (MARCUSSEN, 1953, and ref.). Concerning the complications of BCG vaccination, WALLGREN (1952) remarks that no systemic morbid reactions have been observed. USTVEDT (1952) states that the lesions always heal and that progressive or fatal tuberculous disease does not occur. He believes that one of the great advantages of the vaccination is that it never causes a general reaction.

There seem, however, to be occasional exceptions to these empirical statements. During the last few years some reports have been published of fatal tuberculosis where the disease was put in causal connection with a preceding BCG vaccination.

In 1951 HOLLSTRÖM & HÅRD related a case of tuberculosis in a girl BCG vaccinated a couple of days after birth. She sustained generalized lymphoglandular tuberculosis and disseminated abscesses in most of the organs. The girl died of her disease at the age of 15 months. The bacilli were typed by means of culture and animal experiments. They behaved like typical BCG strains.

A similar case of generalized lymphatic tuberculosis with fatal outcome is reported by MEYER (1953, 1954). His patient was a 9 year old boy who died two years after the BCG vaccination. The bacterial strains were investigated with reference to virulence, morphology, etc. and there was considered to be no doubt about the type (JENSEN, 1954).

[1] Pathology.
[2] Bacteriology.

Another report is given by THRAP-MEYER *et al.* (1954) concerning a 24 year old man who died $4^1/_2$ years after BCG vaccination of lymphogenic as well as haematogenic tuberculosis. The thorough bacteriological examinations, especially the microscopic morphology, indicated BCG (OEDING & HESSELBERG, 1954).

DESPIERRES *et al.* (1951) briefly reported a case of fatal infection in an infant BCG vaccinated at birth by scarification of the arm. A severe glandular reaction occurred involving the regional supraclavicular and cervical lymph nodes which suppurated and discharged a large amount of pus. The patient got fever, deteriorated and died 3 months after the vaccination. No bacteria at all were shown in the pus in spite of microscopy, culture and inoculation experiments. No morbid-anatomical findings were given.

There is practically nothing to show that this case represents fatal tuberculosis caused by BCG and, consequently, it will not be further dealt with below.

This is applicable also to a case reported by BLUMENTHAL (1954) of a boy BCG vaccinated when 1 week old and dead about 7 years later in a generalized amyloidosis. His disease was interpreted as a cutaneous tuberculosis possibly provoked by the BCG vaccination. No tubercle bacilli were found in spite of several biopsies, cultures and inoculation tests. Nor were the pathological findings unquestionable.

The clinical course of the three cases mentioned above does not show any specific signs differing from those of a severe tuberculous infection caused by ordinary human or bovine bacilli. The tuberculin reaction was negative in two of the cases and faintly positive in one (MEYER, 1954). Pathologically, however, they have several features in common and many that are different from those encountered in "ordinary" tuberculosis.

This also holds true in a case of our own, the pathology of which will be discussed later together with the other cases. This case concerns an infant BCG vaccinated when a few days old and dead 8 months later with tuberculosis, most probably caused by BCG.

Clinical Report

The patient was a boy born at term without complications, his birth weight being 2,820 g (Obstetric Journal 853/-52). The 19 year old mother had been hospitalized about three weeks before the delivery because of mild toxaemia. On the fourth day of life the boy was intradermally BCG vaccinated in the left thigh. No complications were encountered during the puerperium, and 10 days post partum mother and child were discharged from the Obstetric Clinic.

The infant was nursed $4^1/_2$ months but after 3 months he had to have increasing amounts of a supplementary formula. For one month (the 6th) he got an extra supply of A and D Vitamins; his food was deficient in vegetables. He developed fairly normally during the first half year of life, apart from generalized eczema which appeared when he was two months old but gradually subsided. No tuberculosis was found in the family or environment in spite of thorough investigations made after the boy's death. No special complications were observed in other children vaccinated with the same batch of vaccine.

Fig. 1. Roentgenogram of the chest ten days before death. Large infiltrations in the left superior lobe and at the bases of both lungs as well as minor infiltrations above the right hilum.

At six months some nodes appeared in the left groin. About four weeks later the boy got a "cold" with cough and fever. He was treated at home with penicillin injections. The fever disappeared but the coughing persisted. There was marked anorexia and the boy lost weight. He developed respiratory difficulties and was therefore admitted to the Pediatric Clinic (Journal 98/-53).

The patient was now in a poor condition, emaciated and dehydrated with reduced weight (4.9 kg) and loss of skin turgor. There were clinical signs of rickets. Respiration was short and puffing, face and hands were subcyanotic. At the site of the BCG injection, in the left thigh, an induration of about 1 × 1 cm could be seen with central necrosis. In the left groin, two or three hard nodes were felt of the size of hazel nuts. The infant had no fever or leucocytosis but a moderately accelerated sedimentation rate and a hypochromic anaemia (Hb 8.1 g/100 ml). The Wassermann reaction was negative. Because of the dermatosis mentioned above no tuberculin test had been performed before admission. His reaction to tuberculin was now found to be negative (Mantoux 0.1 and 1.0 mg). X-ray of the lungs revealed large infiltrations in the left superior lobe and at the bases of both lungs, as well as minor infiltrations above the right hilum (Fig. 1). Mainly coliform bacteria were found in the throat swab. No pathogenic intestinal organisms could be demonstrated.

Oxygen was administered to the boy who became cyanotic as soon as he was out of the oxygen cabin, especially at the feedings. He managed to drink a little but most of his fluid intake had to be administered by catheter and parenterally. His weight went up from 4,900 to 5,300 g within a few days but then decreased again.

The patient received penicillin, later terramycin, and finally streptomycin. However, no beneficial effect was seen in the general condition or the pulmonary lesions.

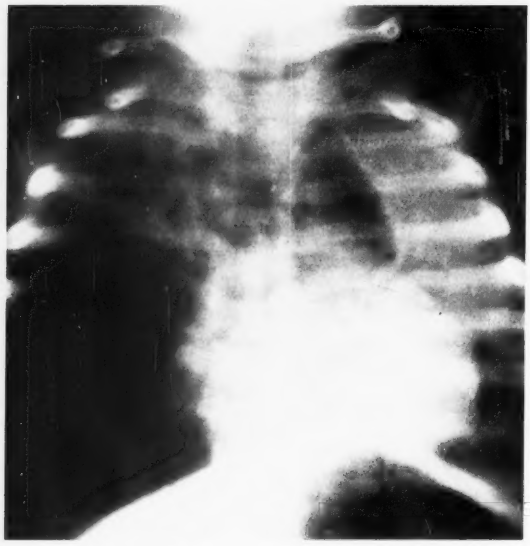

Fig. 2. Roentgenogram of the chest three days before death. The infiltration at the right superior lobe has progressed.

The infiltration in the upper part of the right lung progressed as is seen in Fig. 2. The rickets was treated with large doses of Vitamin D and calcium.

In spite of antibiotics and two blood transfusions the patient's condition grew worse. After ten days his temperature rose to about 40° C. The cyanosis and dyspnoea increased and the boy died on the 12th day after admission.

Autopsy

A complete autopsy was done 36 hours after death.

The body was that of an emaciated 8 months old boy, weighing 5 kg. An ulceration measuring about 1 cm in diameter was found over the lateral aspect of the left thigh at the point of BCG vaccination. The subcutaneous tissue under the ulceration showed caseous necrosis.

The *lungs* were markedly enlarged. The right pleura was opaque with a fine film of fibrin. The left pleura appeared normal. The tracheal and bronchial mucosa was intensely reddened. There was a small quantity of mucopurulent exudate in the large bronchial lumina. No bronchiectasis could be observed. The consistency of the lungs was firm and there were practically no airbearing parts. The lobes were fairly uniform in colour throughout. The dominant colour on the dry sectional surfaces was reddish gray with some mottling of pink and dull red areas. No areas of cavitation or caseation were present and nothing of the translucent, smooth, gray appearance of a "gelatinous pneumonia".

The hilar *lymph nodes* were small and appeared macroscopically normal. The left inguinal, the retroperitoneal and the mesenteric lymph nodes were enlarged and matted together, forming conglomerates, measuring from 1 to 3 cm in diameter. The

consistency was rather firm but the cut surfaces were somewhat bulging, nodular, and of grayish colour. There was no evidence of necrosis or calcification. The lymph nodes in the right groin seemed to be normal.

The *thymus* was very small (6 g).

The *spleen* was slightly enlarged and firm in consistency. Its cut surfaces were deep red and the Malpighian bodies stood out sharply against the red pulp. No caseous necrosis was seen.

The *liver* was of normal size and consistency. Its colour was light grayish-brown with a trace of mottling on the cut surfaces. In the right lobe a whitish focus of soft consistency was present with a diameter of nearly 1 cm.

The epiphyseal ends of the *long bones* showed typical rachitic changes. No craniotabes and no rachitic rosary were found.

The *bone marrow* and the *central nervous system* appeared normal as well as all the other organs. Thus, no signs of miliary dissemination were found.

Cultures were taken at autopsy from the lungs and from a mesenteric lymph node.

Microscopic Examination

Sections of most organs were taken. All blocks were fixed in 10 per cent formalin and stained with VAN GIESON'S stain, hematoxylin and eosin, GRAM'S stain, mucicarmine, LADEWIG'S modification of MALLORY'S stain, ZIEHL-NEELSEN method and with HALLBERG'S method for fungi and acid-fast bacilli (HALLBERG, 1946). Only the significantly affected organs are described.

Typical tubercles and large areas of caseous necrosis were found in the corium and in the subcutaneous tissue at the site of the BCG vaccination. Some of the necrotic areas were fistulating. Myriads of acid-fast bacilli were present in these lesions.

The sections of the *lungs* showed advanced pathologic lesions in practically all parts of the parenchyma. Most alveoli were found to contain amorphous material, which by means of the above mentioned stains was shown to be principally fibrin. Moreover, large numbers of monocytes and alveolar macrophages, smaller numbers of lymphocytes, plasma cells, and eosinophilic and neutrophilic granulocytes were found (Fig. 3). In many places the alveolar exudate was beginning to organize (Fig. 4). The small bronchi were somewhat ectatic with denuded epithelium. The same material was found in the small bronchial lumina as in the alveoli together with the desquamated epithelium. There was a fairly marked oedema around the larger vessels (Fig. 3). The alveolar septa were thickened and fibrotic and were infiltrated with the same inflammatory cells as the contents of the alveoli. No epithelioid tubercles or areas of caseous necrosis were present. Thus, the microscopic picture was rather non-specific. No acid-fast rods could be found in these areas, nor any fungi or specific bacteria.

In the upper lobes, however, there were more advanced lesions. In addition to the pneumonia described above in the other lobes, several round inflammatory foci were present. They averaged 1 cm in diameter and were composed of densely packed lymphocytes, eosinophilic and neutrophilic granulocytes, plasma cells and epithelioid cells. No necrotic areas were seen, but a few multinucleated giant cells of rather uncharacteristic appearance (Fig. 5) and a few small calcified areas were present. The epithelioid cells were sparse and there were no epithelioid tubercles. In these foci a few acid-fast rods were detected in HALLBERG stained sections, but no other bacteria nor any fungi.

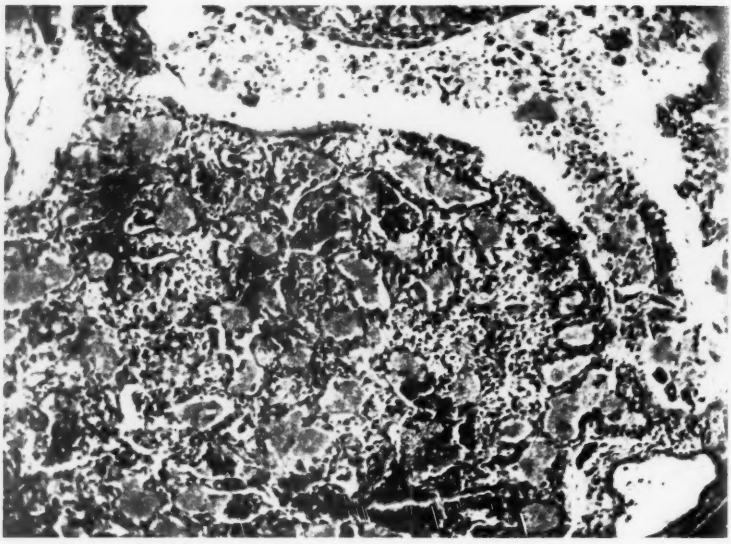

Fig. 3. Section of the lung showing an ectatic bronchus (upper right) with desquamated epithelium, fibrinous material, and inflammatory cells in the lumen. The alveoli are distorted and are filled with fibrinous exudate. There is marked interstitial fibrosis and round cell infiltration throughout. In the upper left corner and in the lower right there is marked oedema around the vessels. Tubercle-like structures are not seen and no acid-fast bacilli or other micro-organisms were found on special stainings in this area. Haematoxylin and eosin. 90.

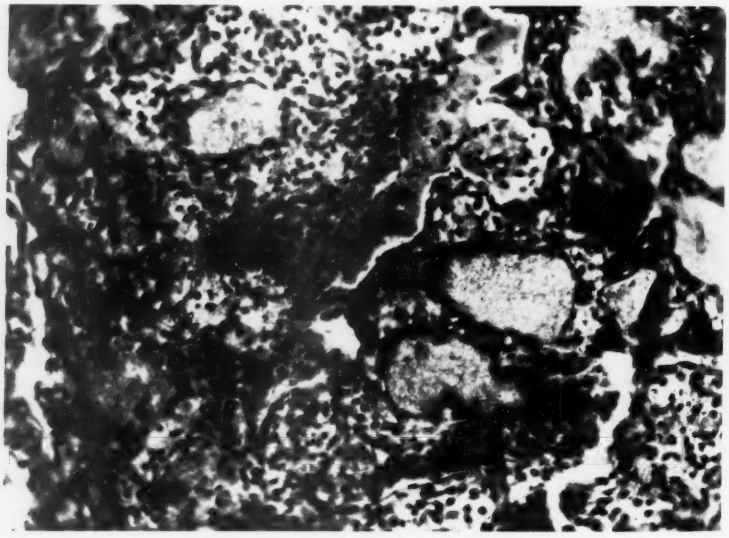

Fig. 4. High magnification of an area of the lung similar to that in Fig. 3. There is [illegible]rly organization of the alveolar exudate. The alveolar septa are thickened. The inflamma[illegible]ory cells are mainly lymphocytes, eosinophilic and neutrophilic granulocytes, and mono[illegible]tes without epithelioid appearance. Thus no evidence of specific inflammation is present. [illegible]AN GIESON stain. ×175.

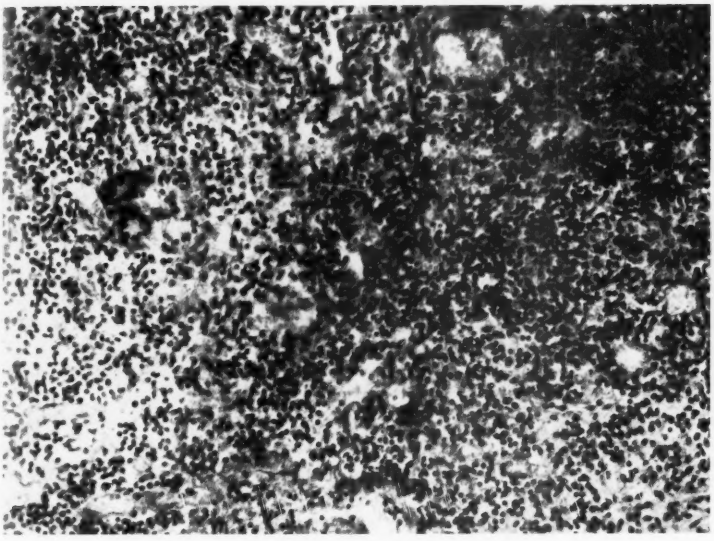

Fig. 5. Section from the margin of one of the inflammatory foci in the upper lobes of the lungs. There is dense infiltration composed chiefly of lymphocytes and monocytes. A few multinucleated giant cells of a rather atypical appearance are seen but no epithelioid tubercles and no necrosis. On special stainings a few acid-fast bacilli were found, but no other micro-organisms. Haematoxylin and eosin. × 175.

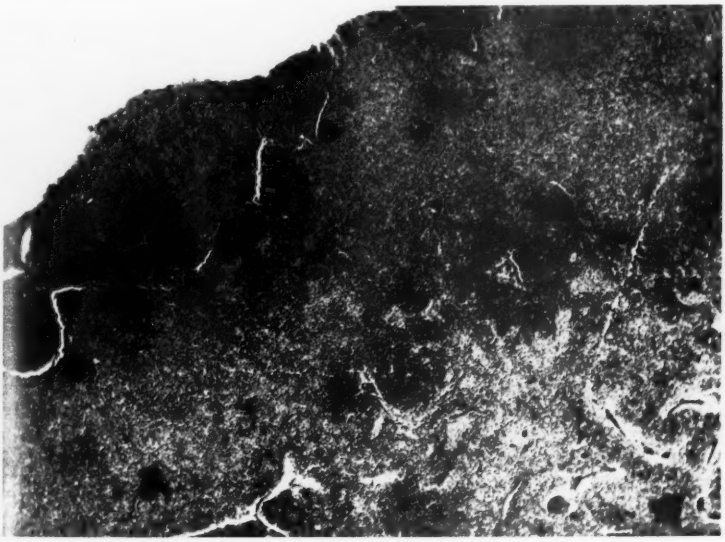

Fig. 6. Mesenteric lymph node. The subcapsular sinus (upper left)—that the capsule is torn off is an artefact—is filled with a plug of densely packed cells. The peripherally situated follicles (dark) are small and irregularly separated from one another by a diffuse overgrowth of pale cells. The central part of the lymph node (lower right) is fairly normal. No caseous necrosis. VAN GIESON stain. × 30.

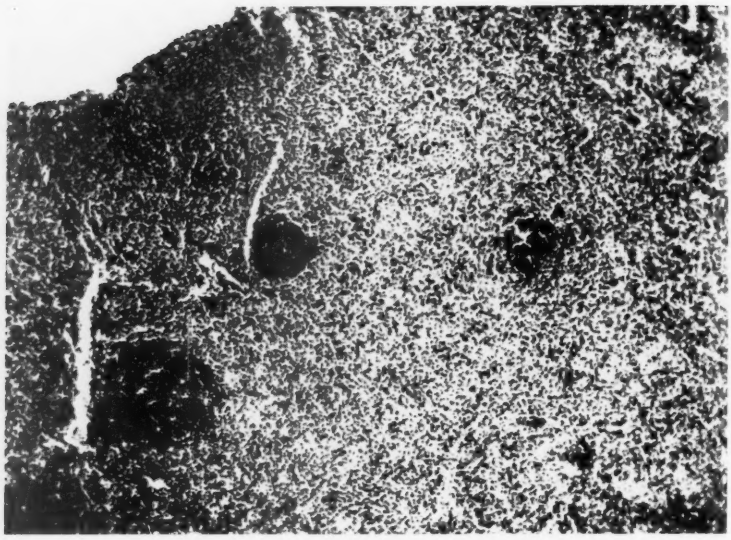

Fig. 7. Higher magnification of Fig. 6. Both the plug in the subcapsular sinus and the diffuse overgrowth of pale cells in the parenchyma consist of epithelioid cells. They have no characteristic arrangement, and no giant cells of the Langhans type are seen. Myriads of acid-fast bacilli were found, with special staining, in the parenchyma as well as in the subcapsular sinus. VAN GIESON stain. × 90.

All enlarged *lymph nodes* showed principally the same microscopic picture. The normal structures in the peripheral part (cortex) were obscured by an overgrowth of epithelioid cells. The follicles were hardly discernible, widely separated and without reaction centres. The subcapsular and cortical sinuses were filled with plugs, mainly consisting of epithelioid cells and lymphocytes. The central part (medulla) was fairly intact (Fig. 6). The epithelioid cells did not form tubercle-like structures and no giant cells or areas of caseous necrosis were found (Fig. 7). There was a moderate periadenitis. As in the inoculation lesions myriads of acid-fast bacilli were present, chiefly in the subcapsular sinuses and in the cortex of the lymph node.

The cortex of the *thymus* was greatly reduced and the gland appeared to be composed largely of medullary tissue. Hassal's corpuscles were almost completely absent. No specific changes were found in the gland apart from a very small patch in a lobule near the surface where there was an overgrowth of irregularly arranged cells of epithelioid type. No giant cells or caseous necrosis were seen (Fig. 8). A fairly large number of acid-fast bacilli was found in the affected area (Fig. 9) but nowhere else in the thymus. There was a sparse fatty infiltration.

The lesions found in the *spleen* were comparatively slight. Most of the lymphatic nodules were of about normal size and shape. Some of them had, however, necrotic centres. No hyalinization was present. The red pulp and the sinuses were engorged with red cells and the walls of the sinuses were moderately prominent. There was an increase also of white cells in the red pulp. Many of these were eosinophilic and neutrophilic granulocytes and there was a moderate number of plasma cells. The

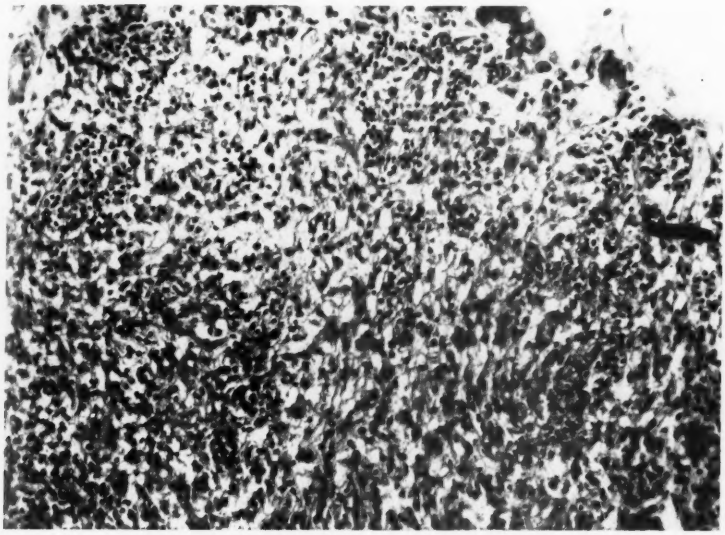

Fig. 8. Section from a small patch in a lobule near the surface of the thymus showing an irregular overgrowth of epithelioid cells. No tubercles or caseous necrosis. The rest of the thymus was very atrophic and contained no epithelioid cells. Haematoxylin and eosin. × 160.

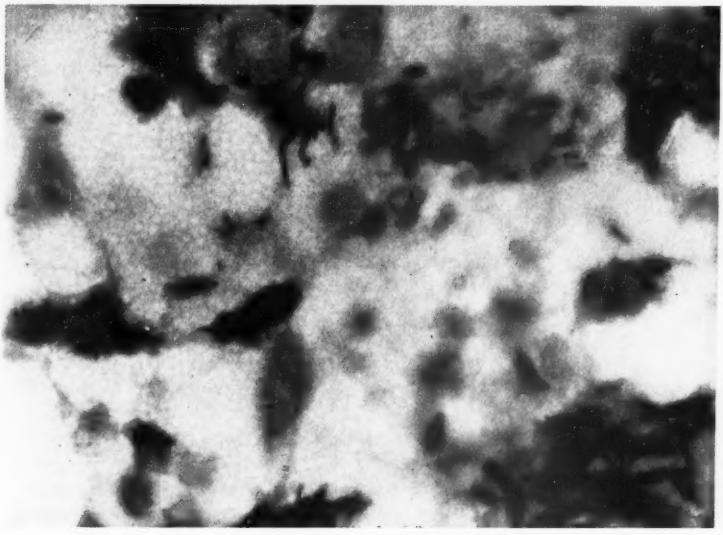

Fig. 9. High magnification of the area in the thymus shown in Fig. 8. Numerous acid-fast rods with typical appearance of tubercle bacilli are present, occurring mostly in groups and some intracellularly. HALLBERG's stain. Oil immersion. × 1600.

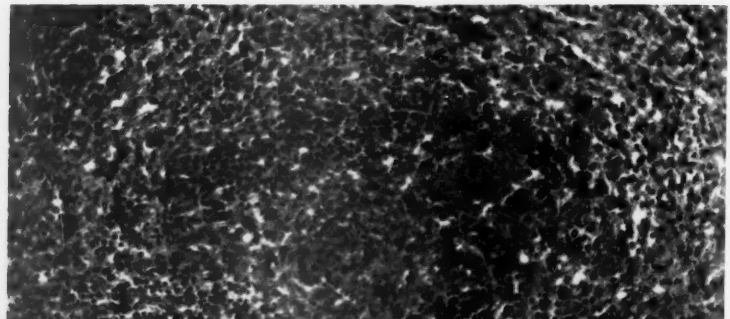

Fig. 10. Section of the spleen showing one of the sparse epithelioid tubercles in the red pulp. The tubercle has a fairly typical appearance with epithelioid cells in the centre of the lesion and a ring of lymphocytes about the periphery. No giant cells are seen, however, and no caseous necrosis. Very few acid-fast rods could be detected with special staining. VAN GIESON stain. × 140.

red pulp contained fairly large amounts of blood pigment in the form of hemosiderin. A few epithelioid tubercles could be detected, but no caseous necrosis was seen. The tubercles seen were, however, of a fairly typical appearance with epithelioid cells and peripheral lymphocytes (Fig. 10). No giant cells were found and the acid-fast bacilli were few and far between and could only be found after prolonged search in the sections stained according to HALLBERG. No other micro-organisms were seen.

The soft, whitish focus in the right *liver* lobe contained densely packed lymphocytes, eosinophilic and neutrophilic granulocytes, plasma cells and monocytes of epithelioid appearance. There was no necrosis, and the relatively sparse epithelioid cells showed no characteristic arrangement. In several portal areas all over the organ there was marked round-cell infiltration. The histologic picture was thus chiefly non-specific. After prolonged search a few acid-fast rods were found in the inflammatory focus, but no other micro-organisms.

Bacteriological Investigations

At the Bacteriological Institute, in Uppsala, acid-fast rods were isolated from the lungs and from a mesenteric lymph node. On Löwenstein-Jensen medium the rods formed typical colonies of the human type of tubercle bacilli. At the same time guinea-pigs were inoculated, but no progressive tuberculosis developed. Repeated tests with guinea-pigs and also with rabbits gave the same results.

Because one could not exclude the presence of BCG, strains from both sites were sent to the Bacteriological Laboratory in Gothenburg for comparison with the BCG used there.

In the following the strains are numbered 4680 and 4681. The investigations are in three parts, (1) Animal tests; (2) Growth on different kinds of media; (3) Attempts to identify the strains by means of enzymatic reactions.

1. Animal tests.

a) Each of the strains 4680 and 4681 was inoculated on eight guinea-pigs with up to 5 mg semidry bacterial mass. One month after the inoculation the animals' reaction to tuberculin was found to be positive (Mantoux 0.1 ml of 1 mg O.T. per ml). At autopsy (6 and 12 weeks after inoculation respectively) no pathological lesions were found in the animals.

b) Each of the strains, 4680 and 4681, was inoculated on two rabbits with 0.01 mg semidry bacterial mass. The animals gained in weight and no tuberculosis was found at section after six (strain 4680) and four (strain 4681) months respectively. The rabbit tests were cut short because two animals died of intercurrent diseases.

Thus, these animal tests, like those at the Bacteriological Institute in Uppsala, show that the strains 4680 and 4681 are in this respect indistinguishable from the BCG-strain.

2. Tests concerning growth on different kinds of media.

a) On Löwenstein-Jensen medium the strains formed "eugonic", greyish-yellow pigmented colonies, which could not be distinguished from colonies of the same shape formed by BCG and tubercle bacilli of the human type. The strains grew at 37° C, but not at 22° C.

b) In common with the BCG-strain, the two strains did not grow in Besredka's medium. The importance of such a finding is emphasized by K. A. Jensen in his report on the bacteriologic investigations of the Danish case of tuberculosis produced by BCG which J. Meyer (1954) has related.

c) On Sauton's medium the strains showed the usual surface growth.

d) The growth in Dubos' fluid medium with different concentrations of Tween 80 was investigated. According to Middlebrook, Dubos & Pierce (1947), BCG and virulent tubercle bacilli show different kinds of growth in this medium depending on the concentration of Tween 80. In Table 1 results are given from a comparative investigation of the strains 4680 and 4681, the BCG-strain, the virulent standard strain H37Rv and the two strains P1 and P2, which were isolated from specimens sent to the diagnostic department. P1 and P2 are both virulent for guinea-pigs. These investigations also show that the strains 4680 and 4681 grow like the BCG-strain. The virulent strains show a clearly different manner of growth.

e) Observations on the surface growth on Dubos' oleic acid albumin agar medium. Middlebrook, Dubos & Pierce (1947), Engbaek (1952) and others have shown that growth on Dubos' solid medium is different for an avirulent mycobacterial strain as compared with that of a virulent one. Virulent mycobacteria have a greater tendency to form cords. This phenomenon can also be observed in cultures on glass slides, according to Pryce, as Oeding (1951) has stated. Oeding & Hesselberg (1954) have paid special attention to this method in the investigation of their case.

The strains 4680 and 4681, the BCG-strain, H37Rv and the two virulent strains P1 and P2 were compared after cultivation on oleic acid albumin agar by direct

TABLE 1

The growth in fluid Dubos' medium with different concentrations of Tween 80.

Strain	% Tween 80					
	0	0,001	0,005	0,01	0,02	0,05
4680	g.	f.g.	f.d.	f.d.	f.d.	f.d.
4681	g.	f.g.	f.d.	f.d.	f.d.	f.d.
BCG	g.	f.g.	f.d.	f.d.	f.d.	f.d.
H37Rv	g.	c.f.	f.d.	f.d.	f.d.	f.d.
P1	g.	c.f.	f.d.	f.d.	f.d.	f.d.
P2	g.	c.f.	f.d.	f.d.	f.d.	f.d.

c.f. = coarse-flocculent growth
g. = granular growth
f.g. = finely granular growth
f.d. = finely dispersed growth

agar microscopy, according to the method of ENGBAEK (1952). The incubation period was 72 hours. At microscopy it was possible to observe growth of principally two types:

Type 1: The cords are heavy and bulky. They grow in manifest coils, which end more or less abruptly. The rods grow in what is generally called "typical serpentine cords".

Type 2: The rods have not the same tendency to grow in coils. The coils that are seen are graceful, and divide into several branches, which are especially marked at the ends of the coils. Thus one cannot see the abrupt ending which is characteristic of type 1.

The H37Rv, P1 and P2 grew like type 1, while 4680, 4681 and BCG grew like type 2.

These experiments were repeated several times. The readings were always made by a bacteriologist uninformed of the origins of the cultures, since the readings could easily be influenced by subjective factors. The above investigations show that on this medium the strains 4680 and 4681 grow in the same way as the BCG-strain.

3. Identification by means of enzymatic reactions.

a) The Catalase reaction. This reaction was performed according to a method demonstrated by MIDDLEBROOK (1954). It was included although it does not permit separating a BCG strain from a virulent human strain. By means of this method it is possible, however, to distinguish between INH-resistant (and sometimes guinea-pigs avirulent) tubercle bacilli and, on the other hand, virulent INH-sensitive bacilli and BCG. This reaction was positive for 4680, 4681, BCG and H37Rv but negative for an INH-resistant strain. These results were expected as sensitivity tests had shown that the strains 4680 and 4681 were as sensitive as H37Rv for INH (no growth on LÖWENSTEIN-JENSEN medium containing 0.1 γ INH per ml).

b) The Neutral Red reaction. The reaction was performed in Dubos' medium as described by DUBOS & MIDDLEBROOK (1948) but without the addition of Tween 80. Instead of Tween 80, the plasma substitute, Periston, was added to the medium. With this reaction no absolutely clear distinction can be made between virulent and

non-virulent strains. However, DUBOS emphasizes that practically all virulent strains give a very strong reaction while BCG-strains become only faint red or colourless. The strain 4680 was only faint red, 4681 was somewhat more red, H37Rv was coloured bright red while the BCG-bacteria remained colourless. Thus, this reaction gave no clear information as to whether the strains 4680 and 4681 were more similar to the virulent H37Rv or to the avirulent BCG.

c) The Arylsulphatase test. The outcome of this test, as described by WHITEHEAD, MORRISON & YOUNG (1952) and WHITEHEAD, WILDY & ENGBAEK (1953), depends on the type of mycobacteria. ENGBAEK (1954) emphasizes that "tubercle bacilli of human and bovine type very seldom give positive reaction, or, if any reaction at all does occur, it is weak. The test is positive with BCG and with tubercle bacilli of avian type". Unfortunately the Swedish BCG-strains seem to give a negative arylsulphatase reaction while the Danish strains of BCG give a positive one. This difference between the strains is now being studied by ENGBAEK (personal communication). The strains 4680 and 4681 gave a negative reaction.

Hence, the bacteriological investigations gave the following result: By most of the special tests related above it was impossible to detect any difference between the bacilli isolated from the patient and the BCG used in Sweden.

To summarize: An 8 month old boy, BCG vaccinated, intradermally, over the left thigh a few days after birth, developed at the age of 6 months regional lymphadenitis followed by progressive, emaciating disease, resistant to therapy. At autopsy, widespread tuberculosis of atypical appearance with extensive lymphoglandular involvement was found with myriads of acid-fast bacilli at the site of vaccination and in the regional, mesenteric, and retroperitoneal lymph nodes. Smaller numbers of acid-fast rods were found in the thymus, spleen, liver and in the upper lung lobes, where a peculiar pneumonia was seen. Obviously, the spread was principally lymphogenous. The bacteriological investigations of cultures taken at autopsy showed that the disease was caused by a low-virulent strain of acid-fast bacilli, indistinguishable from BCG.

Discussion

There is no method which can be regarded as absolutely reliable when one has to decide if a mycobacterial strain is what we call BCG or not. JENSEN has, in the Danish case, paid special attention to the animal tests, while OEDING & HESSELBERG draw their inferences concerning the Norwegian case, not only from animal tests but also to a large extent from *in vitro* investigations. HOLLSTRÖM & HÅRD give no detailed bacteriologic report. We feel that one should make as many different investigations as possible, and when practically all results, as in our case, point in the same direction, there is strong support for the belief that the bacilli may have derived their origin from a BCG-strain used for the production of BCG-

vaccine. However, at the present stage of research we cannot prove that this is the case.

In the four cases (those of HOLLSTRÖM & HÅRD, MEYER, THRAP-MEYER *et al.*, and the present case) the pathologic picture differed from that in "ordinary" tuberculosis in such a way as to affirm the assumption that the tissue reactions were evoked by other strains of tubercle bacilli than the usual ones. A study of the pathology of the cases also gives interesting information from a general pathologic point of view, viz., concerning the theories about the factors which condition the appearance of tissue reaction in human tuberculosis. As three of the cases were children, the pathologic features common to them will be described against the background of the usual picture of tuberculosis in childhood.

In infancy and early childhood tuberculous infection is characterized by a tendency to develop the well-known primary complex with caseous necrosis, both in the primary focus and in the enlarged regional lymph nodes. This is the basis for the second typical manifestation of the tuberculous infection in children—miliary tuberculosis. A more unusual form is the rapidly extending lesion in the pulmonary parenchyma with liquefaction and acute cavitation.

In some respects, there is complete conformity in the pathologic picture of the three topical cases in children (and also in the adult case) to that of tuberculosis caused by the common pathogenic bacilli. Thus, there was in all cases a primary focus at the site of vaccination and the regional lymph nodes were severely involved. So far the picture was the same as that encountered in a usual primary complex in the lungs or the intestines. However, in spite of the great enlargement of the nodes, there was no nodular tissue reaction at all, no formation of giant cells, practically no caseous necrosis, but an overwhelming number of acid-fast rods in the parenchyma. These are features seldom seen, either in the lymph nodes of the primary complex, or in ordinary lymph node tuberculosis.

Other disparities from usual childhood tuberculosis common to the cases under discussion are the lengthy course of the disease and the almost complete absence of caseation and cavitation in the organs. Haematogenous spread with miliary tuberculosis is reported in the case of HOLLSTRÖM & HÅRD, but the typical picture of miliary tuberculosis was not seen in the other cases. In MEYER's case the infection had involved only the lymphatic system. Lymphogenous spread was certainly most important in our case but a haematogenous one could not be excluded.

In two of the pediatric cases (MEYER's and ours), and in the adult one, *the lungs* were severely involved, and the pneumonia was of an interesting character (HOLLSTRÖM & HÅRD give no detailed description of the pul-

monary lesions). The lungs were the seat of widespread lesions of atypical appearance both macro- and microscopically. There were no signs of miliary tuberculosis and the findings were difficult to interpret. In all three cases, acid-fast bacilli were cultured from the lungs, and no other micro-organisms were found. It is, therefore, plausible to suggest that the pulmonary picture was due to BCG. If so, the pneumonia of BCG has its own characteristics, chiefly non-specific in nature.

The peculiar findings in the *lymph nodes* of all the cases may be elucidated by the theories concerning factors which condition the appearance of tissue reaction in tuberculosis. As is well known, the microscopic appearance of the tissue reaction in tuberculous infections depends principally on two factors (GUNN, 1953): the degree of hypersensitivity, and the number of bacilli present in the lesion, which in turn depends on the virulence of the strain and the resistance of the host. The epithelioid cells are considered to be large mononuclear phagocytes which have ingested tubercle bacilli and various disintegration products. The caseous necrosis is particularly found in individuals with hypersensitivity to the tubercle bacillus (tuberculin-allergy) (LURIE, 1932 and FOLLIS, 1938).

The microscopic findings in the lymph nodes of all these cases are in conformity with these theories. Thus, when there was no hypersensitivity clinically (Mantoux reaction negative), no caseous necrosis was seen microscopically, in spite of the overwhelming number of bacilli. In MEYER's case, however, which showed a faintly positive Mantoux reaction, caseous necrosis was found. As mentioned above, the vast number of acid-fast bacilli in the lymph nodes is a feature which is seldom seen in the primary complex or in ordinary lymph node tuberculosis. In view of the proved, unchanged, low virulence of the acid-fast bacilli in all the cases, this feature would mean a low resistance of the body. Moreover, the almost complete absence of nodular tuberculoid reaction in the lymph nodes of all the cases denotes probably an inability to wall off the infection and, thus, a state of low resistance, which is also stressed by WAALER *et al.* (1954). The unusual findings in the lymph nodes are consequently those to be expected in young individuals with faint tuberculin hypersensitivity, or none at all, and with poor resistance, infected with a strain of tubercle bacilli of low virulence.

From a pathological as well as clinical point of view, it is thus highly probable that the cases which obviously succumbed to the "BCG-itis" were in a poor state of resistance against infection. The patient of HOLLSTRÖM & HÅRD showed a positive Wassermann reaction (of unknown etiology), our case was rachitic, and in the case of THRAP-MEYER *et al.*

the sedimentation rate had been accelerated for several years prior to the BCG vaccination.

A "low resistance" constitutes a lack of physical equipment, which, however, might not often be obvious at the time of vaccination and is thus of limited value as a possible clinical contraindication to vaccination.

The authors of the three previous cases of probable BCG-tuberculosis have all concluded that there is no reason to change the practice with regard to BCG vaccination. Of course, these few fatal complications do not overbalance the many million vaccinated without complication. The prophylactic value of the vaccination is too great.

When discussing BCG vaccination one must consider the environment in which the vaccination takes place. The topical tuberculous morbidity is a significant factor, as is pointed out by a Danish author (Ugeskr. for Læger. *115:*1034, 1953): In a tuberculous milieu the importance of the complications is small in comparison with the risks of omitting the vaccination. When the tuberculous threat is less obvious, the complications must play a major role. Even if they are rare, their number becomes *une quantité non négligeable* when the whole population is vaccinated.

Summary

Three cases of fatal tuberculosis in association with BCG vaccination have been published in the literature and a case of our own is reported here. In all the cases the acid-fast bacilli found were indistinguishable from BCG.

All the cases are from Scandinavian countries and have been reported in these last few years. Three of the cases were children. The clinical course did not show any specific signs differing from those of ordinary severe tuberculous infection. The tuberculin reaction was negative in three cases and faintly positive in one.

Pathologically, all the cases have many features in common, and in the three children the findings differ in several respects from those encountered in fatal tuberculosis in children caused by the usual tubercle bacilli. The picture is dominated by a widespread lymph node tuberculosis, mostly of a non-caseous type, with myriads of acid-fast bacilli, but almost completely without nodular tissue reaction with tubercle formation and giant cells. The lungs were also severely involved and two of the pediatric cases showed a peculiar pneumonia. There were histological signs of low resistance against the infection in all the cases.

The significance of the bacteriologic and pathologic findings as well as the clinical importance of these serious complications are discussed.

Tuberculose mortelle suite à la vaccination au B.C.G.

On a publié dans la littérature trois cas de tuberculose mortelle après une vaccination au B.C.G. et l'auteur rapporte un nouveau cas. Dans tous les cas on ne pouvait pas faire la distinction entre les bacilles acido-résistants et le B.C.G. Tous les cas proviennent des pays scandinaves et ont été décrits pendant ces dernières années. Trois d'entre eux étaient des enfants. L'évolution clinique ne montrait pas de signes spécifiques différents de ceux d'une infection tuberculeuse sévère ordinaire. Dans

trois cas la réaction à la tuberculine était négative, dans un cas elle était faiblement positive. Du point de vue anatomo-pathologique tous les cas se ressemblent sous de nombreux aspects. Chez les trois enfants on a trouvé des lésions différentes, sous de nombreux rapports, de celles trouvées dans la tuberculose mortelle de l'enfant causée par le bacille ordinaire de la tuberculose. L'image est dominée par une tuberculose ganglionnaire généralisée, de type en général non-caséifié contenant des myriades de bacilles acido-résistants; la réaction nodulaire du tissu avec formation de tubercules et de cellules géantes était cependant pratiquement absente. Les poumons étaient également fortement atteints et deux enfants présentaient une pneumonie particulière. On a trouvé dans tous les cas des signes histologiques de diminution de la résistance contre l'infection. L'auteur discute la signification de ces données bactériologiques et anatomo-pathologiques, ainsi que l'importance clinique de ces complications sérieuses.

Tödliche Tuberkulose durch BCG-Vaccination.

Drei Fälle von tödlicher Tuberkulose im Zusammenhang mit der BCG-Vaccination sind in der Literatur berichtet worden, und ein neuer Fall wird mitgeteilt. In allen Fällen waren die gefundenen säurefesten Bazillen nicht vom BCG zu unterscheiden. Alle Fälle sind aus den skandinavischen Ländern und wurden in den letzten Jahren berichtet. Drei dieser Fälle waren Kinder. Der klinische Verlauf zeigte keine spezifischen Zeichen, die von denen einer gewöhnlichen, schweren tuberkulösen Infektion abweichen. Die Tuberkulinreaktion war negativ in drei Fällen und schwach positiv in einem Fall. Pathologisch gesehen fand man unter diesen Fällen viele gemeinsame Züge, und in den drei pädiatrischen Fällen weichen die Befunde in verschiedener Hinsicht von denen ab, die man bei der tödlichen, durch den gewöhnlichen Tuberkelbazillus hervorgerufenen Tuberkulose der Kinder findet. Das Bild wird von einer ausgebreiteten Lymphdrüsentuberkulose, von vorwiegend nichtkäsigem Typ, beherrscht, mit Massen von säurefesten Bazillen, aber fast ausschliesslich ohne typische Tuberkelbildung mit Riesenzellen. Die Lungen waren auch schwer betroffen, und zwei der pädiatrischen Fälle zeigten eine besondere Art von Pneumonie. In allen Fällen fand man histologische Zeichen geringer Resistenz gegen die Infektion. Die Bedeutung der bakteriologischen und pathologischen Befunde und die klinische Bedeutung dieser ernsten Komplikationen werden diskutiert.

Un caso fatal de vacunación por el BCG.

Han sido publicados en la literatura tres casos fatales de tuberculosis en conección con vacunación por el BCG y aquí se relata un nuevo caso. En todos los casos los bacilos ácido-resistentes encontrados eran indistinguibles de aqellos del BCG. Todos los casos provienen de los países Escendinavos y fueron relatados en estos últimos años. Tres de ellos eran niños. El curso clínico no mostró ninguna señal especifica diferente de las observadas en una infección tuberculosa grave del tipo habitual. La reacción a la tuberculina fué negativa en tres casos y debilmente positiva en uno. Los hallazgos patológicos tuvieron muchos aspectos en común en todos los casos y en los casos de los tres niños los hallazgos fueron diferentes en varios aspectos de aquellos encontrados en la tuberculosis fatal de los niños, causada por el bacilo tuberculoso usual. El cuadro es dominado por una tuberculosis difusa de los ganglios linfáticos, de un tipo predominantemente no caseoso, con miríadas de bacilos ácido-resistentes, mas casi enteramente sin reacción tisular nodular con formación de tubérculos y células gigantes. Los pulmones estaban también gravemente

comprometidos y dos de los casos infantiles mostraron una neumonia peculiar. Habia signos histológicos de baja resistencia contra la infección en todos los casos. Se discute el significado de los hallazgos bacteriológicos y patológicos así como la importancia clínica de estas serias complicaciones.

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Received 1.12. 1954

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Acta Pædiatrica 44: 237—253. May 1955

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Should Mass Vaccination with BCG be Discontinued in Scandinavia?

by ARVID WALLGREN

In November, 1953, WHO had assembled a group of experts for the purpose of issuing directions for a continuation of the BCG campaign. The Expert Committee, of which I was a member, unanimously concluded that "a specific resistance to tuberculosis can be induced by artificial means (vaccination)". The Committee stated that the value of vaccination would be measured by its capacity to produce an increased resistance, not only in experimental animals, but also in human beings. A report was given of investigations in progress in this respect in the United States of America as well as in Great Britain. The opinion was expressed that in that way light would be shed on the problem of the value of BCG vaccination. While looking forward to the results of these investigations and considering, further, certain distressing events in recent years, I have felt justified in again drawing attention to the problem of the efficacy of BCG vaccination and to the principles of its application.

Natural Resistance to Tuberculosis

In order to establish a proper estimate of BCG and an elucidation of its possibilities and limitations, a few words will have to be said on the question of resistance to tuberculosis in general. It is well known that a natural resistance to tuberculosis exists along with specific immunity. The latter is acquired from previous tuberculous infections. The former is congenital, partly hereditary. For the purpose of arriving at an adequate conception of the significance of specific individual immunity, the degree of nonspecific resistance, its variations and causes will have to be enquired into.

Certain kinds of animals possess a marked resistance to tuberculosis, whether of a human or a bovine type. Others are very sensitive to human-pathogenic mycobacteria of any type. As far as human beings are concerned, they have a very strong resistance to certain tubercle bacilli that will kill an

animal, e.g., Wells' vole bacillus. Also, one human race will differ from another in power of resistance. It is well known that the power of resistance of, for instance, Jewish people is greater that that of non-Jews. Similarly, primitive peoples show a low capacity of resistance as compared to that of highly civilized nations. Even in one and the same country, great variations may occur in resistance among people of the same race in a population. At the beginning of the present century, the ravages of tuberculosis were much more accentuated in Northern Sweden (Norrland) than in Southern Sweden. The explanation was not to be looked for principally in more pronounced risks of infection but rather in a lower power of resistance. Even in a particular locality, some families may be much more liable to succumb to tuberculosis than the majority of other families and their relations. As is well known, the latter fact gave rise to the old conception of the hereditary nature of tuberculosis.

The variations in resistance in various age groups are familiar. It is lowest among the youngest children, increasing towards school-age, again falling at puberty. Another factor that exerts a more lasting effect on the degree of resistance is heredity. This has been particularly obvious from investigations on twins. Among 114 cases of monozygotic twins, of which one of each pair had tuberculosis, 65 per cent of the fellow twins also disclosed tuberculosis. Contrariwise, among 86 dizygotic twins only 21.8 per cent of the fellow twins had tuberculosis.

Owing to a lack of resistance in certain families, a natural selection gradually appears through the extinction of sensitive individuals. Even without any particular measures against tuberculosis, the general power of resistance will grow after some generations, owing to the disappearance of families lacking such a protection (i.e., through the biologic growth of resistance). The remaining population will then come to consist of principally such families as have withstood the tuberculous infection, thanks to their more marked resistance. This applies to all countries with a very low death-rate in tuberculosis—to Sweden, among other countries. The population in those countries possesses a resistance far exceeding that of countries with a primitive and uncivilized population.

Specific Immunity to Tuberculosis

Before entering into the question of the value of BCG vaccination, some references have to be made to an acquired immunity to tuberculosis after a spontaneous infection. The earliest studies of tuberculous immunity were carried out at the beginning of the present century, chiefly by German and American scientists. Gradually, animal experiments disclosed in a con-

vincing manner that a primary infection provides improved protection against subsequent tuberculous infections. In this connection, the following requisites have to be noted: (1) the immunizing primary infection must not be of a rapidly fatal type, (2) the test infection must not be stronger than required for overcoming all the test animals within a reasonable time, and (3) the test infection must not be introduced before the expiration of the incubation period of the primary infection. When all these requirements were duly observed, it was possible to demonstrate in all instances the existence of an acquired, specific tuberculous immunity.

The necessity to observe the above-mentioned conditions and requisites for succeeding in demonstrating an immunity to tuberculosis suffices to show that an acquired specific immunity in the most fortunate circumstances, and even in ideal animal experimental conditions, will only be relative and, accordingly, unable to prevent a strong new infection. Studies of animal experiments also point out some additional important observations for judging the part played by immunity in the course of tuberculosis. In spite of the existence of immunity, an animal may not rarely succumb to tuberculosis.

In what way are the animal experimental observations regarding immunity to tuberculosis to be applied to Man? At the beginning of the present century routine tuberculin tests performed on groups of children showed that the infection rose from zero at the time of birth with such rapidity that all children were infected by the age of fifteen years. While some, in the particularly young age group, fell ill with the primary infection, the majority were unable to tell when the infection had occurred. Healthy, tuberculin-positive children could be exposed to renewed infection from the outside without contracting the disease. Adult persons, like doctors and nurses, at sanatoria for the treatment of tuberculosis did not fall ill with tuberculosis conspicuously more often than the population as a whole in spite of the permanent risk of infection—they were immune through childhood infections.

Nowadays, most children escape infection. As a rule, the primary tuberculous infection occurs at an adult age. Often at the present time, grown-up people, unless BCG-vaccinated, lack specific immunity.

BCG Immunity

This brings us to the question of artificial tuberculous immunity, produced by BCG vaccination. Disregarding occasional critics who, for theoretical reasons and lacking in personal experience, have denied, often somewhat emotionally, the prophylactic value of BCG vaccination, all physicians

who have penetrated the matter at all are probably agreed that a properly performed BCG vaccination produces a specific immunity, increasing the power of resistance to any virulent tuberculous infections. In my opinion, the most perfect arguments in favour of that view have been presented by HEIMBECK, HYGE, DIFFS and DAHLSTRÖM, ARONSSON and DICKIE. On the other hand, those who have presented observations of their own in order to show an alleged lack of effectiveness of BCG vaccination (f. i LEVINE and SACKETT) have, in their turn, been proved to have disregarded such conditions as are generally recognized as indispensable in order to secure immunity before the onset or a virulent infection.

Even though the immunization power and its protective capacity have to be regarded as fully proved, differences of opinion are to be noted regarding the degree and extent of the protection resulting from that immunization process. This was clearly manifested in the course of the discussion in the aforementioned Expert Committee of the WHO. In this connection, misleading or exaggerated statements have not rarely been made. BCG vaccination cannot in itself, as an isolated measure in the campaign against tuberculosis, essentially reduce mortality and morbidity in a country. Animal experiments have shown that this artificial immunity is definitely weaker in its effect than that produced by virulent infections. There is, as a matter of course, no reason to suppose that the BCG bacillus would, in this respect, behave otherwise in a human being.

BCG Vaccination and Primary Tuberculosis

Clinical experiences show that BCG-induced immunity is only relative. I have not, so far, observed a single case of clinical primary tuberculosis directly originating from a superinfection of a person previously primarily infected, and who is a carrier of a specific immunity from tuberculosis. Contrariwise, I have had occasion to treat a great number of BCG-vaccinated children ill with a syndrome of primary tuberculosis in immediate connection with a virulent infection, in spite of actual BCG immunity, confirmed through a positive tuberculin reaction.

There is no difference between a postvaccinal primary tuberculosis in its origination and a primary tuberculosis in those not subjected to BCG. One gets the impression that a more benign course of tuberculous disease exists in those vaccinated. However, in the absence of any direct material for comparison, the impression of benignity in a postvaccinal primary infection is decidedly subjective. In order to form a reliable opinion it would be necessary to know how a primary infection without previous vaccination would have behaved in that very child.

Accordingly, from the above, it will be obvious that BCG immunity is weaker in its effect than that occurring after a virulent primary infection and that, consequently, it will not provide the same degree of protection as the latter against a primary tuberculosis or an air-borne virulent infection. The significance of a BCG vaccination, on the other hand, must not be belittled considering that the number of cases of manifest primary tuberculosis after a virulent infection in BCG-vaccinated persons is extremely small in comparison with all observations of the lack of manifest primary tuberculosis, in the face of definite virulent exposure. The authors mentioned above may be referred to.

BCG Vaccination and Early Postprimary Diseases

In all likelihood, BCG vaccination will also play a certain part in diminishing the risk of early postprimary tuberculous diseases, particularly meningitis and miliary tuberculosis. Since virulent primary infections, nowadays, mostly occur at an age when these diseases are very rare in Sweden, it is, however, difficult to prove this observation. Most cases of meningitis and miliary tuberculosis occur during the first 3–4 years of life. According to recent information from the Head Medical Officer of the Public Schools in Stockholm, Dr. U. HJÄRNE, only 1 % of the children in that city are infected at 7 years of age, 3.7 % at 10 years and 5 % at 15 years of age. Simultaneously with the decline in primary infections during childhood in our country, miliary tuberculosis and tuberculous meningitis have become more and more uncommon. For several years I have not been in a position to demonstrate to my students a single fresh case of meningitis. It is no wonder that no vaccinated child has come under my care with that disease. The fact that we have not observed a single case of miliary tuberculosis or tuberculous meningitis in adequately BCG-vaccinated children, cannot serve as proof that significance should be attributed to BCG vaccination in this regard. Many instances can attest to the fact that meningitis and miliary tuberculosis *may* also occur in children who have been BCG-immunized, when primarily infected and shortly afterwards fallen ill. The reduction in the frequency of meningitis in the countries of Northern Europe, *may*, however, *partly* be connected with BCG-immunization. The latter prevents more or less effectively a reaction in most cases of virulent primary infection. The growth and spread of the tubercle bacilli are checked by immunization, and this may have to be taken into account also with regard to meningitis and miliary tuberculosis.

As far as other types of postprimary diseases are concerned, DIFFS and DAHLSTRÖM's investigations seem to indicate that pleurisy occurs less often

in BCG-vaccinated cases than in others. The frequency of pleurisy has always been considerably higher than miliary tuberculosis and meningitis. For this reason, it should be easier to ascertain differences in this respect between vaccinated and unvaccinated cases. Moreover, pleurisy is a more common disease in such age groups as are nowadays primarily infected than in younger age groups that, at the present time, escape such infections.

A third type of early postprimary disease is found in tuberculosis of the lungs that appears as a direct, local and immediate progression from such foci as arose at the time of the primary infection. This type of tuberculosis of the lungs has attracted increasing attention, the more the primary infections have been postponed towards higher age groups. A progressive postprimary pulmonary tuberculosis is, of course, extremely infrequent in children before the age of puberty. Formerly, it occurred, occasionally, in infants and young children, deficient as they are in natural resistance. Today, primary infection is transformed into progressive pulmonary tuberculosis only when it occurs at, or after, the age of puberty. A suggestion that offers itself almost immediately is that a progressive pulmonary tuberculosis will more often originate from primary pulmonary tuberculosis when the reaction produced in the respective lung is particularly marked, thus indicating an inferior power of resistance in those infected, than when a pulmonary reaction is absent or insignificant. Considering that a BCG vaccination can obviously preclude, to a large extent, severe reactions in the parenchyma of the lungs, it is tempting to accept, on purely theoretical grounds, the contention that vaccination should be able to prevent progression from the pulmonary foci. DAHLSTRÖM and DIFFS have shown that the frequency of early postprimary pulmonary tuberculosis in BCG-vaccinated cases falls somewhat below that of non-vaccinated soldiers. Here, however, it should, be emphasized that the boundaries between pulmonary tuberculosis, resulting from a direct progression from a primary tuberculous focus, and other forms of postprimary tuberculosis are, no doubt, indistinct.

Immunity to Tuberculosis and Late Postprimary Tuberculous Diseases

We now approach the question of the possibility of precluding late postprimary disease by the use of BCG vaccination. Since tuberculosis of the bones and joints, as well as urogenital tuberculosis, occurs comparatively rarely, it is difficult to obtain any commensurable material for ascertaining the frequency in vaccinated and unvaccinated groups, respectively. No doubt, all doctors possessing experience with these diseases will know that both these localizations of postprimary tuberculosis *may* occur even among BCG-vaccinated people. The still very common late postprimary pulmonary

tuberculosis is more important, i.e. the type of disease that has not appeared as a direct progression of primary tuberculosis. It is a well-known fact among specialists on tuberculosis that it *may* attack even those who have been BCG-vaccinated. The General Secretary of the Swedish Association Against Tuberculosis has provided me with some figures of the incidence of pulmonary tuberculosis in BCG-vaccinated persons. Out of 5,000 patients in Swedish hospitals for tuberculosis, 5 per cent had been BCG-vaccinated. It is as yet not definitely established whether it occurs less often in a population among those vaccinated than among those not subjected to vaccination. DAHLSTRÖM has not found a significant difference in the incidence of pulmonary tuberculosis in vaccinated and unvaccinated conscripts. It is impossible to draw any *definite* conclusions as to whether or not a reduction in mortality and morbidity in tuberculosis over a long period of time originates in a nationally enacted system of BCG vaccination. The Tuberculosis Research Office of the WHO in Copenhagen has devoted much attention to this question which has been particularly studied in Finland. There, in 1948, a vaccination *en masse* of people under 25 years of age was carried out, and the vaccination has since continued in accordance with the same principles. The conclusion arrived at is that the reduction in mortality in tuberculosis after the introduction of the BCG vaccination does not exceed that noted in countries where BCG vaccination is but slightly, or not at all, practised.

For purely theoretical reasons it seems improbable that a BCG immunization would be of any noteworthy significance with regard to a decrease in morbidity in late postprimary pulmonary tuberculosis. Earlier, the question of the relationship between the first appearance of pulmonary tuberculosis and a congenital deficiency in resistance has been discussed. It is easy to prove that a specific immunity is of little importance in this connection, or that a lack of natural resistance prevails over any protection from immunity. Anyone who develops late postprimary pulmonary tuberculosis, has for a long time been the bearer of an immunity produced by a primary infection. It would be difficult, it seems to me, to imagine that BCG immunity which, no doubt, is less effective than that resulting from a virulent infection, would, in this respect, be able to do more than the latter. In this instance, as in the case of an early postprimary pulmonary tuberculosis, there is no question of a direct continuation of the process in the pulmonary foci. As a rule, it probably proceeds rather from foci of tubercle bacilli dispersed by different ways from the primary focus. Irrespective of the localization of primary tuberculosis, which may be anywhere in the lungs, the great majority of cases of tardive postprimary tuberculosis originate in the apexes. The tubercle bacilli cannot have arrived there other than by

dispersion from a primary focus in a person who is specifically immunized against tuberculosis. Evidently, the forces favouring a tardive postprimary tuberculosis of the apexes are much stronger than the specific immunity that until then held the tubercle bacilli in check. If this statement is accepted, then the significance of BCG vaccination in counteracting pulmonary tuberculosis must be seriously questioned. Still, pulmonary tuberculosis is the principle form of tuberculosis, entirely dominating morbidity and mortality in Sweden. BCG vaccination cannot, therefore, be assumed to have contributed noticeably to the continuous fall in the death-rate of tuberculosis. Other factors have decided the outcome.

Reasons for the Marked Fall in Tuberculosis Mortality

What factors may have influenced mortality in tuberculosis in the present century? At least some of them can be registered, but others, in accordance with recent findings, may have been contributory. In Sweden, the following reasons for the reduction in mortality may be noted:

I. *General increase of resistance to tuberculosis.*
   a. Biologic factors.
   b. Social-hygienic conditions.
II. *Shift in time of primary infection from the most delicate ages of childhood.*
   a. Decrease of sources of infection.
   b. Improved public enlightenment and new stipulations.
III. *Earlier diagnosis and treatment.*
   a. Rational organization of dispensaries.
   b. Improved availability of hospital beds and increased knowledge.
IV. *More effective therapy.*
   a. Chemotherapy.
   b. Surgical therapy.
V. *BCG vaccination.*

From the above it may be concluded that *the essential aim of BCG vaccination is to counteract the effect of primary infections and complicating tuberculous disease.* The question arises whether the protection offered by mass vaccination against the most common form of tuberculosis, viz., late postprimary progressive tuberculosis of the lungs, has any particular significance in the fight against tuberculosis.

Value of BCG Vaccination Varies under Different Circumstances

In countries where the primary infections develop early in childhood, the manifest forms of primary tuberculosis and the early postprimary diseases

(meningitis and miliary tuberculosis) are common. In those countries general BCG vaccination is definitely indicated, and as early as possible. This applies to all the countries with a high morbidity in tuberculosis where as yet no, or but small, measures have been taken to cope with the disease and its distribution. The opposite occurs in Sweden where the primary infection takes place in childhood in but a very small number of cases. In the former, each adequate BCG vaccination may perhaps prevent manifest severe primary tuberculosis and, to a very great extent, its immediate consequences, viz., miliary tuberculosis and meningitis. In those cases, therefore, BCG vaccination must be of considerable importance.

In countries with late primary infections and satisfactory resistance, the great majority of BCG vaccinations will never exert a protective influence during childhood. In other words, they become relatively unnecessary. Out of a thousand cases vaccinated (for example as newborns), only about a hundred will become infected at all, most of them at an age when the primary infection is generally benign and seldom involves any immediate malignant sequelae. Among these 100 children, only 25 to 50 are likely to have a primary tuberculosis calling for clinical treatment. Further, the vaccination might have been ineffective in preventing manifestations of disease in some of the cases owing to the fact that the immunity had been lost or not sufficed to increase the resistance. Accordingly, only a very small number of all the children subjected to routine mass vaccination will profit by BCG vaccination. The question now arises whether mass vaccination in childhood is worthwhile. Always, in taking steps of a prophylactic nature, the positive has to be weighed against the negative, viz., gain and advantages versus costs and drawbacks. The negative factors involved are the costs of vaccine preparation and distribution and the doctor's examinations. Also, tuberculin tests before and some time after vaccination should be mentioned, both requiring at least two visits. Finally, the loss of time has to be considered. Moreover, in many instances the visits to the doctor have to be made over and over again. This applies to cases where the tuberculin check-up after vaccination failed to show positive results and the test, or even the vaccination, has to be repeated, perhaps one or more times in order to obtain the ultimate response.

All the above-mentioned costs and inconveniences, and perhaps also others, are of no great importance if by BCG vaccination, in a country where tuberculosis is rare, the life of a certain number of children or of a few adults can actually be saved, or invalidity prevented. Even when 99 are submitted unnecessarily to the inconvenience, trouble and costs of BCG vaccination in order to provide the 100th with the assurance of survival and health, a risk-free mass vaccination must be regarded as well justified.

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In this connection, the term "mass vaccination" is used for vaccinations in Sweden of all newborns at the maternity hospitals, of all tuberculin-negative school-children, of the whole population or of groups of the population in connection with mass micro-radiographic examinations, etc. It may of course be inferred that the vaccination of newborns is a very simple and inexpensive procedure, requiring no preliminary tuberculin tests, with the children already available at the maternity hospital. The same applies to some extent to school children who, in all circumstances, are subjected to tuberculin tests. Owing to the presence of a staff, no time is lost through tuberculin check-ups after vaccination.

Is BCG Vaccination Harmless?

Such an easily performed and inexpensive procedure should, it has been said, be universally employed, since, in any case, the method of vaccination is harmless and may offer protection. It is impossible to say at any time when, in a civilized society, a child may be exposed to infection. All doctors who have promoted the application of BCG vaccination have never failed to stress its absolute harmlessness. Earlier, in fact, we had every excuse for maintaining such a view since there were no grounds for suspecting serious harm or complications from the procedure. The formation of abscesses at the spot of injection was not considered, nor the suppurative lymphadenitis that now and then will appear for one reason or another. In his study of the BCG campaign that the three Scandinavian countries initiated after the war, USTVEDT, among the many millions of vaccinated people, failed to trace a single case in which the vaccination process could be proved harmful. It should be emphasized that, at the time of the aforementioned investigation, a sufficient number of laboratories were not available. In addition, the equipment of those in existence was unequal to the demand for careful bacteriologic study or threatened complications as is now deemed essential. Such bacteriologic control renders it possible to prove that harmful effects may result from BCG vaccination.

In fact, at that time, there was such a general conviction regarding the harmlessness of BCG vaccine, that complaints of alleged complications after the execution of vaccination were not very seriously considered.

Ever since BCG vaccination began to come into more widespread use, the possibility of complications has always been kept in view in our country. The Swedish National Association Against Tuberculosis has promoted studies on such subjects, by providing travel and expense grants for the observation of cases of a suspected character in special hospital departments. At my clinic, we have treated a series of children with alleged or

actual BCG complications, consisting, in all instances, of large abscesses at the site of injection or, in a few cases, at the regional glands. After a short hospitalization they have been sent home as cured.

In our country, even though no further evidence has been forthcoming of any likely harm in BCG vaccination from many points of view, in Swedish BCG medical circles it has, nevertheless, been well known from certain observations that, in spite of everything, the BCG bacilli are not quite so apathogenic as was supposed.

It has been possible to produce a progressive tuberculosis in the hamster by causing injury, beforehand, by the administration of silicon to the lungs or by depriving the animals of their resistance through infections, or in other ways. Certain experimental conditions may render the BCG bacilli pathogenic even in mice.

It is fairly remarkable that when it has been shown for the first time that BCG may occasionally cause serious progressive processes also in Man, it is left to the Scandinavian countries to provide that information. It is remarkable in that the population obviously possesses an excellent power of resistance. From Denmark, as well as from Norway and Sweden, information of fatal BCG processes, after adequately performed vaccination, is now available. In proportion to the more than one hundred million vaccinations that have been performed so far in the whole world, the few reported instances of complications cannot be regarded as being very weighty. They are, however, to be regarded as a minimum number of cases and should be considered in relation to the annual number of BCG vaccinations in the country in which they have occurred. However, in the individual case, the fatal outcome of a process undertaken for the purpose of preventing a disease, has to be looked upon as an immensely deplorable misfortune, a catastrophe. In no instance has it been possible to show that there has been any reason why the victim reacted in this noteworthy manner. The BCG bacilli, *per se*, cannot be suspected since a great many vaccinations have been carried out with the same vaccine without harmful effect. Nor has it been possible to ascertain that the vaccinators have been guilty of neglect or error. It is an unavoidable conclusion that those vaccinated have, in some way or other, harboured a deficit of resistance to BCG. These patients, very likely, would have disclosed very slight resistance in the event of a virulent tuberculous infection, also.

Today, we are aware of the fact that some individuals are unable to form antibodies or antitoxins. This is obvious from their deficiency in gammaglobulin (agammaglobulinemia) and the absence of reaction to infections from, e.g., streptococci or staphylococci (non-appearance of AST and ASTA) and antidiphtherial vaccination. Such cases are extremely rare. So

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far, about twenty are supposedly known, including 3 from Sweden. Possibly, the very persons in whom BCG has proved pathogenic have been among those exceptional cases. However, in the case described by IMERSLUND and JONSEN, no agammaglobulinemia was noted. It is hardly possible to find protection against such accidents since the individuals do not disclose anything, apart from a predisposition to infection, that sets them apart from other people.

The knowledge that such progressive BCG disease may occur unavoidably shakes our belief in the supposed harmlessness of the BCG bacilli. It is no longer possible to pretend that the BCG vaccination is always harmless. Up to now, we have insisted that as many as possible should subject themselves to BCG vaccination even in the absence of manifest risk of exposure. We are no longer justified in including the harmlessness of the vaccine among our arguments. Reference has been made to vaccination against smallpox. It is obligatory and performed on all children. It cannot be regarded as harmless since, during the past fifty years, more fatal cases have been reported in Sweden in postinfection encephalitis than in smallpox itself. Nevertheless, the vaccination against smallpox goes on. Still, it is misleading to compare the effect of vaccination against smallpox with that of BCG vaccination. The former process gives reliable protection for a number of years against an often fatal disease; the latter one against the immediate effect of a usually innocent primary infection for, perhaps, a similar period.

In a society like ours that has advanced a very long way towards the complete uprooting of tuberculosis and where the resistance of the population is strong, BCG-protection is bound to become less important from one year to another.

The Future of BCG Vaccination

Assuming for a moment, for the sake of argument, that the practice of BCG vaccination was suddenly discontinued in our country, circumstances in general being what they are, we need not fear a return of the mortality that existed a quarter of a century ago. No doubt, we would note an increase in the morbidity in primary tuberculosis, but I very much doubt that we would note a rise in the curve of mortality. Conditions, as they were in our country before the introduction of BCG vaccination, are no longer comparable, but we may perhaps draw conclusions from developments in other countries where BCG vaccination has not been practised, or, at any rate, on such a small scale that it cannot be of any general significance from the point of view of mortality or morbidity in tuberculosis. This applies to a

number of countries, such as Iceland and England and some states in the U.S.A.

To prevent misinterpretations, I wish to emphasize that, when reference to BCG vaccination was made here, it pertained only to general BCG vaccination—a vaccination, *en masse*, of all tuberculin-negative people, whether risk of exposure exists or not. I am not questioning the need, use or value of individual BCG vaccination in cases where the danger of exposure is particularly marked (e.g., in children living in tuberculous surroundings, or among people engaged in certain trades). I would be inclined to regard it as neglect not to vaccinate tuberculin-negative children, when any relatives suffer from pulmonary tuberculosis, even should it be regarded as no longer active. I would consider it equally erroneous to omit the vaccination of student nurses, or medical students, or the staff at a sanatorium or other hospital institution where people with tuberculous disease may be admitted. From the point of view of armed preparedness it can also be regarded as just and important to strengthen resistance among military conscripts. It is never possible to state beforehand which of infected tuberculin-positive soldiers may develop postprimary pulmonary tuberculosis, thus becoming infectious among tuberculin-negative companions. In collective garrison life and with privations at the time of conscription or a state of war, the general power of resistance is also apt to be reduced. This is an additional reason to compensate the loss of resistance by induced specific immunity.

Summary

The natural nonspecific resistance against tuberculosis is the most powerful factor for the protection against tuberculous disease and is probably the sole determinant for the development of the most frequent and, from a mortality point of view, the most important form: postprimary pulmonary tuberculosis. Specific immunity seems to have little or no influence on the degree of resistance against this disease. All those who acquire postprimary tuberculosis are bearers of specific immunity. The specific immunity produced by a tuberculous infection is stronger than the immunity after artificial BCG-infection. Therefore, there is no reason to believe that BCG vaccination could decrease the morbidity rate of postprimary pulmonary tuberculosis any more than the specific immunity after primary tuberculous infection. The decline of tuberculous morbidity and mortality from pulmonary tuberculosis in a country, therefore, cannot be due to BCG-mass-vaccination.

Specific immunity is more or less effective against the immediate consequences of new exogenous infections. Comparison of vaccinated and unvaccinated groups shows that the vaccinated are to a high degree protected against clinical primary tuberculosis and to a certain degree also against the early postprimary diseases: miliary tuberculosis, meningitis, pleurisy, and local progression of primary tuberculous lesions of the lungs.

The increased resistance produced by BCG immunity is of the greatest value in age groups with a very low natural resistance, i.e. infants and small children, and in

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children who run the evident risk of being exposed to tuberculous infection. In a country with a very high tuberculous morbidity, all children are in danger of being exposed and most of them are infected; many at very early age. In such a country, the need of BCG mass-vaccination should be emphasized and vaccination performed on all tuberculin negative children—the sooner the better in order to protect infants and small children. In a country with a very low tuberculous morbidity, only a few children are infected by sources of infection in the home surroundings, most of them not before school-age, i.e. at an age with high natural resistance. In such a country, the need of mass-vaccination may be justly questioned because only a minute fraction of all vaccinated become exposed. The great majority of children have never had an opportunity to profit by BCG immunity and have thus been unnecessarily vaccinated, with all the cost and inconveniences this procedure may imply. BCG vaccination should be confined to selected groups in the population who are in danger of being infected (home contacts, nursing personnel, medical students, conscripts, etc.). The severe or fatal accidents and complications after BCG vaccination that have recently been reported from the Scandinavian countries make it still more desirable to reconsider the present principles of BCG vaccination in countries with a very low tuberculosis morbidity and mortality.

Doit-on changer les principes de la vaccination en masse au B.C.G. en Scandinavie?

La résistance naturelle non-spécifique contre la tuberculose joue le rôle le plus important dans la protection contre la tuberculose et est probablement le seul facteur déterminant du développement de la forme la plus fréquente et, du point de vue de la mortalité, la plus importante : la tuberculose pulmonaire post-primaire. L'immunité spécifique semble n'avoir que peu ou pas d'influence sur le degré de résistance contre cette maladie. Toutes les personnes atteintes de tuberculose post-primaire sont porteurs d'une immunité spécifique. L'immunité spécifique produite par une infection tuberculeuse est plus forte que l'immunité produite après une infection artificielle au B.C.G. C'est pourquoi, il n'y a aucune raison de croire que la vaccination au B.C.G. puisse diminuer davantage le taux de morbidité de la tuberculose pulmonaire post-primaire que l'immunité spéfique après l'infection tuberculeuse primaire. La diminution de la morbidité par tuberculose et de la mortalité par tuberculose pulmonaire dans un pays ne peut donc pas être imputée à la vaccination en masse au B.C.G. L'immunité spécifique est plus ou moins efficace contre les suites immédiates de nouvelles infections exogènes. Une comparaison entre des groupes vaccinés et non-vaccinés montre que les vaccinés sont généralement protégés contre la tuberculose primaire clinique et, à un certain degré aussi, contre les manifestations post-primaires précoces de la maladie : la tuberculose miliaire, la méningite, la pleurésie et la progression locale de la tuberculose pulmonaire primaire. L'augmentation de la résistance produite par l'immunité du B.C.G. est de la plus grande utilité dans des groupes d'âge ayant une résistance naturelle très faible, c.-à-d. chez des nourrissons et des jeunes enfants, et chez des enfants qui courrent le risque évident d'être exposés à une infection tuberculeuse. Dans un pays à morbidité par la tuberculose très élevée, tous les enfants courrent le danger d'être exposés et la plupart d'entre eux sont contaminés, beaucoup à un très jeune âge. Dans un tel pays on devra insister sur la nécessité qu'il y a de vacciner en masse au B.C.G. et il faudra vacciner tous les enfants ayant une réaction tuberculinique négative — le plus tôt sera le mieux, afin de protéger les nourrissons et les jeunes enfants. Dans un pays à morbidité par tuberculose très basse, seuls quelques enfants sont contaminés par des sources d'infection provenant des environs du logis, la plu-

part d'entre eux pas avant l'âge d'école, c.-à-d. à un âge où il existe une forte résistance naturelle. Dans un tel pays on est en droit de se demander si une vaccination en masse est nécessaire puisque seule une très petite partie de tous les vaccinés seront exposés à l'infection. La grande majorité des enfants n'a jamais eu l'occasion de tirer profit de l'immunité par B.C.G. et ont donc été vaccinés sans nécessité, tout en occasionnant des frais et des inconvénients que ce procédé peut apporter. La vaccination au B.C.G. devrait être limitée à des groupes choisis de la population courrant le danger d'être contaminés (contact au logis, personnel infirmier, étudiants en médecine, les conscrits, etc.). Les accidents graves ou mortels et les complications suite à une vaccination au B.C.G., décrits récemment dans les pays scandinaves, montrent qu'il serait très souhaitable de reconsidérer les principes actuels de la vaccination au B.C.G. dans des pays à morbidité et mortalité par tuberculose très basse.

Sollen Massenimpfungen mit BCG in Skandinavien fortgesetzt werden?

Die natürliche unspezifische Resistenz gegen Tuberkulose ist der stärkste Faktor zum Schutz gegen tuberkulöse Erkrankung und ist wahrscheinlich die einzige Determinante für die Entwicklung der häufigsten und — vom Mortalitätsstandpunkt aus gesehen — der wichtigsten Form: der postprimären Lungentuberkulose. Spezifische Immunität scheint wenig oder gar keinen Einfluss auf den Widerstandsgrad gegen diese Krankheit zu haben. Alle, die eine postprimäre Tuberkulose erwerben, sind Träger von unspezifischer Immunität. Die spezifische Immunität, die durch eine tuberkulöse Infektion erzeugt wird, ist stärker als diejenige nach künstlicher BCG-Infektion. Deshalb besteht kein Grund anzunehmen, dass BCG-Impfung die Morbiditätszahl der postprimären Lungentuberkulose mehr herabsetzen könnte, als es die spezifische Immunität nach primärer tuberkulöser Infektion vermag. Der Rückgang von Morbidität und Mortalität der pulmonären Tuberkulose in einem Land kann deshalb nicht der BCG-Massenimpfung zugeschrieben werden. Spezifische Immunität ist mehr oder weniger effektiv gegen die sofortigen Folgen einer neuen exogenen Infektion. Ein Vergleich zwischen geimpften und nichtgeimpften Gruppen zeigt, dass die Geimpften zu einem hohen Grade gegen klinisch auftretende primäre Tuberkulose und zu einem gewissen Grade ebenfalls gegen die frühen postprimären Erkrankungen, wie Miliartuberkulose, Meningitis, Pleuritis und lokale Ausbreitung des primären tuberkulösen Herdes in den Lungen geschützt sind. Die durch BCG-Immunität hervorgerufene Resistenzsteigerung besitzt ihren grössten Wert in Altersgruppen mit sehr geringer natürlicher Resistenz, d.h. bei Säuglingen und Kleinkindern sowie bei Kindern, die einem ausgesprochenen Risiko der tuberkulösen Infektion ausgesetzt sind. In einem Land mit sehr hoher Tuberkulosemorbidität besteht für alle Kinder eine Ansteckungsgefahr, und die meisten von ihnen sind infiziert, viele in sehr frühem Alter. In solch einem Land sollte die Notwendigkeit einer BCG-Massenimpfung hervorgehoben werden und eine Impfung bei allen tuberculin-negativen Kindern durchgeführt werden — je früher, desto besser, um Säuglinge und Kleinkinder zu schützen. In einem Land mit sehr niedriger Tuberkulosemorbidität aber werden nur wenige Kinder auf dem Wege der Infektion im Familienkreis angesteckt, die meisten im Schulalter, d.h. in einem Alter mit hoher natürlicher Resistenz. In einem solchen Lande kann die Notwendigkeit einer Massenimpfung in der Tat diskutiert werden, da ja nur ein geringer Anteil aller Geimpften angesteckt wird. Die grosse Majorität der Kinder hat niemals Gelegenheit gehabt, von der BCG-Immunität zu profitieren und ist damit unnötig geimpft worden, mit all den Kosten und Umständen, die eine solche Prozedur mit sich bringt. BCG-Impfung sollte in ausgewählten Bevölkerungsgruppen, welche einer Infektionsge-

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fahr ausgesetzt sind (Infektionsquelle im Familienkreis, Pflegepersonal, Medizinstudenten, Kasernierte usw.) ausgeführt werden. Die schweren oder fatalen Zwischenfälle und Komplikationen nach BCG-Vaccination, die kürzlich von den skandinavischen Ländern mitgeteilt wurden, machen es noch mehr wünschenswert, die augenblicklichen Prinzipien der BCG-Impfung in Ländern mit sehr niedriger tuberkulöser Morbidität und Mortalität einer Überprüfung zu unterziehen.

¿ Debe interrumpirse en Escandinavia la vacunación en masa con BCG?

La natural resistencia inespecífica contra la tuberculosis es el factor más importante para la protección contra esta enfermedad, y es probablemente la única determinante del desarrollo de la más frecuente, y desde el punto de vista mortalidad, más importante de sus formas: la tuberculosis pulmonar postprimaria. La inmunidad específica parece tener poca o ninguna influencia en el grado de resistencia contra esta enfermedad. Todos aquellos que adquieren una tuberculosis postprimaria son portadores de inmunidad específica. La inmunidad específica producida por una infección bacilar es más fuerte que aquella adquirida después de una artificial infección BCG. Por esto, no hay razón para creer que la vacunación BCG pueda disminuír la tasa de morbilidad por tuberculosis pulmonar postprimaria más que la inmunidad específica conferida por una infección primaria. La declinación de la mortalidad y la morbididad por tuberculosis en un país no puede ser debida a la vacunación en masa con BCG. La inmunidad es más o menos efectiva contra las consecuencias inmediatas de una nueva infección exógena. La comparación de grupos de vacunados y no vacunados muestra que los primeros están en alto grado protegidos contra la tuberculosis primaria clínica y en menor grado contra las complicaciones postprimarias tempranas: tuberculosis miliar, meningitis, pleuresía y evolución local del complejo primario pulmonar. El aumento de la resistencia producido por la inmunidad BCG es de gran valor en grupos que corresponden a edades con baja resistencia: lactantes y niños pequeños, y en niños que corren riesgo evidente de exponerse a la infección tuberculosa. En países cuya morbididad tuberculosa sea muy alta, todos los niños corren peligro de infección, estando la mayoría infectados desde edad temprana. En dichos países debe insistirse sobre la necesidad de vacunación BCG en masa, vacunándose a todos los niños tuberculino negativos lo antes posible, protegiendo de esta manera a lactantes y niños pequeños. En países con baja morbididad tuberculosa, solo algunos niños contraen la infección en contactos vecinos al hogar, la mayoría de ellos en la edad escolar, es decir cuando poseen una alta resistencia natural; en dichos países, la necesidad de vacunación BCG en masa puede dudarse ya que será pequeña la fracción de vacunados expuesta a contagio. La gran mayoría de los niños nunca han tenido oportunidad de aprovechar su inmunidad BCG y fueron por lo tanto inútilmente vacunados, con los inconvenientes y costo que implica este procedimiento. La vacunación debe ser limitada a pequeños grupos de población que corran peligro de infección (contactos domiciliarios, enfermeras, estudiantes de medicina, conscriptos, etc). Los graves y fatales accidentes por vacunación BCG publicados recientemente en Escandinavia obligan a pensar seriamente en reconsiderar los principios de esta vacunación que rigen en países con baja morbi-mortalidad tuberculosa.

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Received Dec. 1, 1954.

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Acta pædiatrica 44: 254—262. May 1955

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Acute Cerebellar Ataxia in Children

by G. BERGLUND, H.-O. MOSSBERG, and B. RYDENSTAM

Acute cerebellar ataxia is a disturbance of the central nervous system which is essentially manifested by the acute onset of ataxic symptoms. Attention was mainly directed to this syndrome in children by the studies of GRIFFITH, 1916–1921. Subsequently, more than 50 cases have been described, inter alios by BABONNEIX (1928), KLINGMAN & HODGES (1944), KELLER & KARELITZ (1948), and GOLDWYN & WALDMAN (1953).

The age of the patients ranges from 1 to 12 years, with the majority in age group 2–4. In many cases the symptoms begin suddenly in apparently healthy children, but in other instances, in association with various acute infectious diseases, such as measles, scarlet fever, influenza and poliomyelitis. The prominant feature of the picture is ataxia with cerebellar disturbance of gait, agitation of the head, trunk and extremities, intention tremor, ataxic speech, and nystagmus. Active tendon reflexes, weakness, and personality changes are often noted. Commonly the spinal fluid is normal but slight pleocytosis is observed occasionally. The electroencephalogram in one of KELLER & KARELITZ' cases was pathological, the curve showing mesencephalic involvement, which is in good agreement with the clinical symptoms of the case. The prognosis commonly is favourable and the duration of the disease often less than one month, rarely exceeding 3 to 4 months.

In the following are presented 6 cases of cerebellar ataxia treated in 1953 at the Samariten Children's Hospital, the Hospital for Infectious Diseases, and the Pediatric Clinic, Karolinska Sjukhuset.

Case Reports

Case 1: Sam. 49 04 22. 110/53. A $3^{9}/_{12}$-year-old girl. No family history of nervous or mental disease. Normal development. History of pertussis, 1951, and uncomplicated upper respiratory infections. The onset was sudden: on the morning of Jan. 24, 1953, the child was unable to raise her head on awaking, and refused to turn it sideways. The following days she lay with her head persistently turned to the left, and was

entirely nursed in bed. She was afebrile, had no signs of upper respiratory infection, and ate well. On entry to the Samariten Children's Hospital, Jan. 28, 1953, she was apprehensive and frightened and lay with her head constantly turned to the left. She was gradually persuaded to move her head slightly. Passively, her head had mobility in every direction. No nuchal stiffness. Kernig's and Lasègue's signs negative. Reflexes normal. Tone and turgor normal. Gait staggering and cerebellar-ataxic. Movements of eyes, face and tongue normal. No nystagmus. Afebrile. Fundi and media normal. Lumbar puncture and fluid: pressure normal, 8.8 mg % total albumin, no cells. X-ray of skull, neck and thoracic spine: normal conditions. EEG: activity curves within normal limits.

The patient was hospitalized 3 weeks and placed on penicillin the first 2 weeks. Discomfort from the cervical and thoracic spine persisted one week after admission; the patient refused to turn her neck and was rather hyperesthetic. Her gait was improved, but still ataxic, rather unsteady but with no sideward deviation when she was blindfolded. Rapid improvement followed; two weeks after entry there was free mobility of the neck, regression of the hyperesthesia, and normal gait. Romberg negative. On discharge Feb. 18, 1953, one month after the onset, she was cheerful and alert, walked and ran normally, and revealed an entirely normal nervous status. When seen April 9, 1953, 2½ months after the onset, the patient was alert and healthy, showing normal reactions in every respect. Complement fixation reaction in convalescent serum showed a positive reaction: $^1/_{20}$ against influenza B, negative against influenza A. Repeated tests, Jan. 22, 1954, showed unchanged titer against influenza B. — When seen April 5, 1954, rather more than a year after discharge, the child was alert and well, had not been ill during the passed year, and showed no clinical signs of disease. However, she was more sensitive and irritable and more ill-tempered than prior to her disease.

The present case is typical of cerebellar ataxia: sudden onset with no prodrome and with manifest cerebellar-ataxic symptoms. Except for some residual mental instability the child showed complete recovery after one month. The complement fixation reaction against influenza B was positive in convalescent serum. Acute phase serum was not tested. The correspondent test against influenza A was negative. Complement fixation reaction against polio was not tested.

Case 2. Sam. 51 10 23. 134/53. A $1^3/_{12}$-year-old boy. No family history of nervous or mental disease. Normal development. Since the age of 9 months alternating convergent strabismus, especially of the right eye. Vaccination for smallpox at 11 months was uneventful and the child showed no personality changes afterwards. Onset of present illness at 15 months, in mid-January, 1953, 2 weeks prior to admission. Without any previous signs of infection he had suddenly become peevish and fretful, walking unsteadliy with frequent falling. He did not seem to be in pain and had not sustained any trauma, as far as was known. After a week or so, episodes of agitation of the entire body were noted, but no actual cramps. On entry to the Samariten Children's Hospital, Feb. 3, 1953, the patient was unaffected but fretful, refusing examination angrily. No signs of infection. Tone and turgor normal. No nuchal stiffness. Lasègues' sign negative. Alternating convergent squint, especially of right eye. No nystagmus. Facial movements and active movements of extremities normal, but

nearly constant agitation of different parts of the body. Gross power seemed normal, but he reeled on standing and was unable to walk without support, swayed and fell. Ambulating with support, his gait was uncertain and swaying. He was eager to sit up in bed. Reflexes active and equal bilaterally. Fundi and media normal. Lumbar puncture and fluid: normal pressure, 18 mg % total albumin, no cells. Skull X-ray normal. EEG: frequencies normal for the age.

The child was hospitalized 2 months. The course showed slow regression. On discharge April 2, 1953, his gait was better, though still staggering and wide-based, and support was necessary. Arms and hands showed no ataxia, but on exertion there still was agitation of head and extremities. Reflexes active, equal bilaterally. No clonus.

When seen April 15, 1953, 3 months after the onset, there was continued improvement but the agitation persisted. Complement fixation reaction against influenza in convalescent serum showed titer $^1/_{20}$ against influenza A, negative against influenza B. Repeated test June 5, 1953, showed titer $^1/_{10}$ against influenza A.

When seen April 13, 1954, over a year after the acute phase of disease, there was further improvement and the child had been well during the past year. There was occasional slight agitation of the head, though quite insignificant. Of late he had been more irrascible and unbalanced and was constantly nervous and sensitive. The complement fixation reaction against polio was negative for all three forms of polio.

This case shows the onset common in cerebellar ataxia: sudden onset without prodrome and with manifest cerebellar ataxic symptoms. The child also exhibited marked agitation of head and extremities, especially after mental or motor exertion. More than a year after the acute phase of disease tremor of the head was noted occasionally. Furthermore, the child was more unstable mentally than previously. The complement fixation reaction against influenza A was positive in convalescent serum, and disclosed that the patient had undergone an influenza infection during an unknown period. Acute phase serum was not tested. Correspondent reactions against influenza B and polio were negative.

Case 3. Epid. 48 06 13. I.K.A. 3872/53. A 5-year-old girl. No family history of nervous or mental disease. Developmental history normal; the child had always been healthy. Prior to the present illness neither the patient nor anyone else in the family had had a cold or signs of other disease. One evening, Sept. 2, 1953, the patient began to complain of headache and seemed tired. The next day she was unable to stand and had shaking movements of the entire body. Admission Sept. 3, to the Hospital for Infectious Diseases. She was alert and afebrile but irritable and fretful. Pharynx slightly reddened but no other signs of infection. No nuchal stiffness. Lasègue's sign neg. The slightest attempt towards movement and the least irritation provoked coarse tremor-like vibrations of head, trunk and extremities. When let alone the patient commonly lay calm and quiet without tremor. Attempts to stand released intense tremor of the entire body and the patient was unable to walk. On attempts to ocular fixation she exhibited rapidly oscillating nystagmus. Speech was abrupt and laboured. Paresis was not demonstrable. Patellar and Achilles reflexes active and equal bilaterally. Abdominal reflexes normal. Babinski normal. Fundi and media normal. Lumbar puncture and fluid: normal pressure, 17 mg % total albumin, 7 cells/mm^3, sugar q[illegible]-

tient normal. EEG showed slow dysrhythmia, indicating moderate cerebral dysfunction. Complement fixation against polio, Sept. 9: type 1 $^1/_{16}$, type 2 $^1/_4$, type 3 $^1/_4$, all positive.

The patient was hospitalized one month. Definite improvement was noted already one week after admission. The tremor and nystagmus disappeared first. Her gait still was rather unsteady and Romberg's sign was positive 2 weeks after admission, but the EEG was normal. Three weeks after admission the patient was completely free from symptoms, with normal gait; Romberg's sign was negative. Complement fixation against polio Sept. 18: type 1 $^1/_4$, type 2 $^1/_2$, type 3 $^1/_2$; all positive. Oct. 3: type 1 $^1/_4$, positive, types 2 and 3: negative. In serum, Sept. 18, were established neutralizing antibodies against type 1 but not against types 2 and 3. Faeces test, Sept. 19, showed growth of cytopathogenic agent type 1.

When seen 2½ months after the onset the patient was completely well, except for some psychic instability. She was also in good health at check-up March 3, 1954, 6 months after the onset. The complement fixation against polio was negative for all three types. Complement fixation against influenza was not performed.

This case is typical of cerebellar ataxia: sudden onset without prodrome and with distinct cerebellar ataxic symptoms, and marked initial tremor of the entire body on the slightest irritation or attempt towards movement. The electroencephalogram showed dysrhythmia which subsided rapidly, as did the tremor. The child made a complete recovery in one month. One week after the onset the complement fixation reaction was positive against polio, Types 1–3, subsequent tests showed a significant decrease of titer for Type 1. One month after the onset only the reaction against polio, Type 1, was positive and 6 months after the onset all were negative. In the acute phase, neutralizing antibodies against polio, Type 1, were established, and faeces tests showed growth of polio virus Type 1.[4] Complement reactions against influenza were not performed.

Case 4: Epid. 50 03 31. 3904/53. A 3½-year-old boy. No family history of nervous or mental disease. Developmental history was normal and the child had previously been healthy. Coincidently with the onset of the child's disease his mother had for a few days had fever, headache and pain at the back of her head. On Sept. 5, 1953, the patient seemed tired and went to bed earlier than usual. The next day he had agitations, first of the head and then of arms and legs. He was unable to stand or walk. Even in bed he complained that he was falling. According to his mother his eyes darted from side to side. At entry, the same day, to the Hospital for Infectious Diseases, the patient was mentally alert, unaffected, and afebrile. With exception for slight pharyngitis there were no signs of infection. No nuchal stiffness, but Lasègue's signs positive at 80°. Attempts towards movement and every sensory stimulus elicited irregular tremor of head and extremities. He was able to walk with support but his gait was reeling, wide-based and cerebellar-ataxic. His speech was quavering and jerky. Finger-to-nose and heel-to-knee tests fumbling. On attempts to ocular fixation there was oscillating horizontal accomodation nystagmus in every direction. No paresis. Tendon reflexes active. Abdominal reflexes normal. Babinski normal. Fundi and media normal. Lumbar puncture: normal pressure, 38 mg % total albumin,

2 cells/mm³. EEG pathological with abnormal basic rhythm. Complement fixation against polio Sept. 9: type 1 1/4, type 2 1/4, type 3 1/4, all positive. Faeces test, Sept. 10 showed growth of cytopathogenic agent of type 1.

The patient was hospitalized one month. Improvement was rapid. One week after admission both tremor and nystagmus had disappeared, but the gait was still rather unsteady. Repeated EEG 10 days after entry showed normal findings. Complement fixation reaction against polio Sept. 18: type 1 1/8, type 2 1/4, type 3 1/4, all positive. Neutralizing antibodies against type 1 were established, but not against types 2 and 3. On discharge the patient was completely free of symptoms.

When seen after discharge he has been completely well, without neurological symptoms, but with greater mental instability than before his illness, April 26, 1954: complement fixation against polio types 1, 2 and 3 and against influenza A and B were negative.

The above case is typical of cerebellar ataxia: sudden onset without prodrome. The patient's mother had a brief episode of fever and headache coincidently with the onset of his disease. The child had distinct cerebellar ataxic symptoms, with agitation of the head and extremities, and nystagmus. The electroencephalogram was pathological, showing abnormal basic rhythm, but was completely normalized at a repeated examination 10 days later. The patient made a complete recovery in one month but was mentally more unstable than earlier. The complement fixation reaction against polio Type 1 showed significant changes of the titer. Faeces test, Sept. 10, showed growth of cytopathogenic agent of Type 1. Neutralizing antibodies were established against Type 1, but not against Types 2 and 3. Reactions against influenza tested in April 1954, were negative.

Case 5. KS 50 05 21. A 3-year-old boy. No family history of nervous or mental disease. Development had been normal and the child had previously been healthy. Onset, April 9, 1953, of fatigue and subfebrile temp. April 14 there was pain in the legs, twitching of hands and arms and somnolence. April 15 the child was admitted to the Hospital for Infectious Diseases. He did not respond on examination, tonus of the extremities was increased, the arms and lower legs were nearly rigid and the feet hyperextended. The pharynx was slightly reddened. Heart, lungs and abdomen showed no abnormality. No nuchal stiffness. Reflexes normal.

On April 16 the patient was referred to the Pediatric Clinic, Karolinska Sjukhuset, on the tentative diagnosis of tetany. On admission he was ill and somnolent. When supported he stood in the position of a spastic diplegic with inwards rotation of the feet and hyperextension of the toes, and with the head in extreme backward extension. Nuchal stiffness was still absent. His arm movements were ataxic and pronounced intention tremor was present. Babinski probably positive bilaterally, Rossolimo likewise. For the rest, the reflexes were normal. Speech was poor on the day of admission and the next day there was total aphasia. Fundi and media normal. Lumbar puncture: fluid normal. Skull X-ray and encephalography showed normal findings. EEG normal.

The patient was hospitalized 7 weeks. Chloromycetin was administered. The course was afebrile throughout. Progression during the first week with increase of tremor and nystagmus on ocular fixation horizontally. Babinski positive on left, uncertain

on right side. After another week, showing slow improvement with decreased tone, slow regression of intention tremor and slow return of speech; 56 mononuclear cells were established in spinal fluid. After yet another week EEG showed slow frequencies. After a month the spinal fluid was normal and the patient showed definite improvement. He then had two attacks of generalized cramps with unconsciousness, lasting about 30 min. EEG was normalized again. Faeces test for C-virus were negative on 2 occasions. Complement fixation against parotitis was neg. Complement fixation against influenza in the acute phase: influenza A $< 1/5$, influenza B $1/10$; in convalescent serum: influenza A $1/5$, influenza B $1/20$. Toxoplasmosis negative. On discharge, June 5, the patient's speech was rather jerky but with coherent sentences; there was still some slight spasticity in the legs. He had received physiotherapy treatments, which were to be continued in his home. Follow-up examination, July 13, showed continued improvement. There was still some motor restlessness, but there had been no further episodes of cramps. Except for a stutter his power of speech was good. No paresis. Babinski doubtful, remainder of reflexes normal. EEG still dysrhythmic, but showed normal frequencies in Nov., 1953.

This case belongs to the composite cerebro-cerebellar ataxias, showing increased tone of the extremities, somnolence, ataxia, and intention tremor. There was initial progression with increase of tremor, nystagmus, increase of cells in spinal fluid, and EEG with slow frequencies. Two episodes of generalized cramps occurred in the course of clinical improvement. Spinal fluid and EEG showed gradual return to normal. Five months after the onset there was improvement but not complete recovery. Tests for C-virus were negative on 2 occasions. Complement fixation reaction against influenza B was positive but showed no significant changes of the titer. Complement fixation reactions against influenza A, parotitis, and toxoplasmosis were negative. Correspondent reactions against polio were not performed.

Case 6: KS 49 05 25. A 4-year-old boy. No family history of nervous or mental disease. Development normal. At 4 months of age he had had severe pertussis and was under medical supervision the first 2 years of life, because of enlargement of the thymus gland. Feb. 19, 1953, he had an acute onset of fever, headache and lumbar pain, and Feb. 22 an outbreak of urticarial rash which disappeared after a couple of days. After a week the patient was afebrile but still had muscular pains, and had become more apathetic. Admission to the Pediatric Clinic, Karolinska Sjukhuset, March 2, 1953. He was in a condition of general irritation. The pharynx was somewhat reddened. There was equal mobility of arms and legs, but he refused to sit up. Moderate intention tremor present. No nuchal stiffness. Abdominal reflexes absent, patellar reflex weaker on right leg. Achilles reflex uncertain. Fundi and media normal. Lumbar puncture: 76 mg % total albumin, max. 3 mononuclear cells, sugar and chloride values normal. Faeces test for C-virus negative. Paul-Bunnel test: $< 1/16$. EEG normal.

The patient was hospitalized 6 weeks. The course was afebrile throughout. The first week he was extremely apathetic and EEG was dysrhythmic. When the muscular pain began to subside, after a week or so of hospitalization, paresis of the lumbar musculature and distinct ataxia appeared. Three weeks after entry the intention

tremor had disappeared completely and EEG was normalized. On discharge, April 16, there was no definite paresis and all cerebellar symptoms had disappeared. The reflexes were normal and the spinal fluid albumin was 31 mg %. Follow-up examinations, May 4, and Sept. 17, showed normal conditions. The patient had been rather fumble-fingered the first month after discharge. EEG, taken at check-ups was rather dysrhythmic for his age.

This case is atypical of cerebellar ataxia. The onset with fever, headache and pain in the small of the back is not the classical picture. The child gradually became more apathetic and intention tremor appeared. The abdominal reflexes were lacking and the right patellar reflex was weakened. EEG showed transitory dysrhythmia. When, after 3 weeks, the muscular pains subsided, paresis of the lumbar musculature and distinct ataxia appeared. After 2 months, the paresis and all cerebellar symptoms had disappeared. Culture for C-virus was negative. Complement fixation reactions were not performed against influenza or poliomyelitis.

Discussion

Cerebellar ataxia is a syndrome which in the more typical cases exhibits symptoms only from the cerebellum. Occasionally however, symptoms are noted suggesting that also the cerebrum is affected. The frequent association with preceding infectious disease has commonly led to the conclusion that the pathologico-anatomical causation is encephalitis with localization to the cerebellum. KLINGMAN & HODGES discuss the term "acute non-suppurative disturbance of the nervous system" but also consider that anamnesis and course in some cases suggest an acute infectious, post-infectious, or closely related process in the nervous system. These authors have attempted to establish neutralizing antibodies for various types of virus, but with negative results.

The 6 cases described above illustrate the clinical picture with exclusively cerebellar symptoms in some cases, in other cases spino-cerebro-cerebellar symptoms, and also the infectious pathogenesis. Cases 1, 3 and 4 illustrate the classical form with cerebellar symptoms only. Case 2 has furthermore an uncommonly pronounced tremor of lengthy duration, Case 5 exhibits spasticity and somnolence, and Case 6, paresis.

The present cases occurred at a time of year with a high incidence of influenza A and B and of polio in the general population. In three cases (3, 4, and 6) polio was diagnosed with certainty: in Cases 3 and 4, virus and neutralizing antibodies against polio Type 1 (Brunhilde) were established, and the complement fixation showed significant titer changes against polio Type 1; and in Case 6, paresis occurred. In Cases 1, 2 and 5 the complement

fixation reaction was positive against influenza A and B, respectively. Significant changes of the titer were not demonstrable, however, for which reason the influenza etiology cannot be proven.

The clinical picture in the unquestionable polio cases showed a mild course while the three cases with suspected influenza etiology had a protracted course, rich in symptoms. The assumedly different etiology of these cases might possibly be the explanation to the difference in the clinical course.

The cases presented illustrate the infectious pathogenesis of the affection. It has long been known that poliomyelitis occasionally exhibits a picture with cerebellar ataxic features (MEDIN) and also that ataxia, spasticity and paresis may appear in combination (WERNSTEDT). It is probable that other pathogenic microorganisms, such as influenza, also may be etiologic. Acute cerebellar ataxia should, therefore, be interpreted as a syndrome with heterogeneous infectious etiology.

In the differential diagnosis, trauma, intoxications, vascular lesions, chronic hereditary ataxia and disseminated sclerosis must be taken into consideration. A most important aspect is to exclude neoplasm in the posterior fossa and the brain stem: this may present difficulties, as seen by the following case.

A 7-year-old girl (Sam. 46 07 05, 469/54) without any preceding signs of infection, was taken ill with cerebellar ataxic disturbances of gait, vertigo and mental indolence. Two weeks after the onset she was admitted to the Samariten Children's Hospital. She had a cerebellar ataxic gait, some difficulty in deglutition, and thick speech. The fundi were normal, the spinal fluid showed no abnormality. Repeated EEG and oto-neurological examinations showed non-specific reactions only. The complement fixation reaction against polio type 1 showed raised titers in 2 tests. After 4 weeks of hospitalization with slow improvement of speech and gait there appeared spasticity of the left side of the body, and some time after discharge vomiting and deterioration began, after which the diagnosis of brain tumor was clear.

Summary

Acute cerebellar ataxia is a syndrome with heterogeneous etiology. The present paper describes 6 cases. Three cases exhibited cerebellar-ataxic symptoms only, two had symptoms indicating that the process affected the cerebrum also, and in one case there were also spinal symptoms (paresis). In three cases the causation was unquestionably polio infection with significant serological tests and pareses. In two of the remaining cases the infectious agent possibly was influenza B, and in the third case, possibly influenza A was responsible. The difference in the severity of the clinical picture between the unquestionable polio cases and the other cases is pointed out. The difficulty of differentiating between tumor of the posterior fossa or the brain stem is illustrated by an additional case, in which the onset initially was in complete agreement with the symptomatology of acute cerebellar ataxia.

Ataxie cérébelleuse aiguë chez l'enfant.

L'auteur rapporte six cas, dont trois présentaient uniquement des symptômes d'ataxie cérébelleuse, deux avaient de plus des symptômes de lésions cérébrales et un avait même des signes d'atteinte médullaire (parésie). Dans trois cas la cause était une infection manifeste de poliomyélite (mise en évidence du virus, parésie). Dans deux autres cas l'agent pathogène était peut-êret l'Influenza B et dans un troisième cas peut-être l'Influenza A. L'auteur insiste sur les différences qui existent dans le tableau clinique et son degré de gravité. Pour illustrer la difficulté de faire le diagnostic différentiel avec une tumeur intracranienne de la fosse postérieure et du bulbe, il rapporte un cas où les symptômes du début correspondaient à ceux d'une ataxie cérébelleuse.

Akute Kleinhirnataxie bei Kindern.

Besprechung von 6 Fällen, von denen drei nur Symptome von Kleinhirnataxie, zwei gleichzeitig andere Symptome (cerebrale Läsionen) zeigten und ein Fall, bei dem sogar spinale Zeichen (Paresen) vorhanden waren. In den 3 Fällen war die Ursache offensichtlich eine Poliomyelitisinfektion (Virusnachweis, Paresen). In den anderen Fällen war die Infektion wahrscheinlich ausgelöst durch Influenza B und im 3. Fall wahrscheinlich durch Influenza A. Die Unterschiede im klinischen Bild und der Schwerheitsgrad werden betont. Die Schwierigkeiten der Differentialdiagnose gegenüber einem intrakranialen Tumor im Bereich der Fossa posterior oder des Hirnstammes werden durch Besprechung eines Falles dargestellt, bei dem die Krankheitszeichen und Symptome anfänglich mit denen einer cerebellaren Ataxie übereinstimmten.

Ataxia cerebelosa aguda en niños.

Se refieren seis casos: tres de ellos tenían solamente síntomas de ataxia cerebelosa, dos de ellos síntomas adicionales y uno de ellos lesiones cerebrales y signos medulares (paresia). En tres casos fué una evidente infección a polio (se demostró el virus, paresias). En los otros casos la infección fué producida posiblemente por virus B de Influenza, en el tercer caso posiblemente por el virus Influenza A. Se pusieron en evidencia diferencias en el cuadro clínico y en su grado de severidad. Las dificultades en el diagnóstico diferencial frente a tumores intracraniales de la fosa posterior o del pedúnculo son ilustradas por un caso en el cual los signos y síntomas iniciales corresponden a los de la ataxia cerebelosa.

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Received Dec. 9, 1954

Samariten Children's Hospital
Stockholm

Acta Pædiatrica **44**: 263—271. May 1955

Clinique Infantile de Karolinska Sjukhuset, Stockholm

La Sténose Hypertrophique du Pylore chez le Nourrisson Prématuré

par G. VAN OOTEGHEM

Plusieurs auteurs (FAXÉN, RÄIHÄ et YLPPÖ, MALMBERG, DURAND) ont remarqué que la sténose hypertrophique du pylore (S.H.P.) frappe surtout les nourrissons dont le poids de naissance est élevé. Selon YLPPÖ la maladie serait rare chez le prématuré. Aussi les cas isolés de S.H.P. chez le prématuré ont-ils été l'objet de nombreuses communications. Exception faite de l'étude récente de KAPLAN et DOBROWOLSKI on ne trouve dans la littérature aucune revue d'ensemble de nombreux cas de S.H.P. chez le nourrisson prématuré.

Nous basant sur un grand nombre de cas de S.H.P., nous avons tenté d'évaluer sa fréquence chez l'enfant prématuré et étudié l'influence de la prématurition sur la symptomatologie, le diagnostic et le traitement de cette affection. Dans ce but nous avons compulsé tous les dossiers de S.H.P. des années 1934 à 1954 se trouvant dans les archives de trois services de pédiatrie de Stockholm : 174 cas de l'Hôpital Samariten, 144 cas de la Clinique Infantile de Karolinska Sjukhuset et 120 cas de l'Hôpital Sachs. Nous avions en outre à notre disposition les dossiers de 265 cas hospitalisés de 1922 à 1942 dans l'Hôpital des Enfants Malades de Göteborg. Les derniers cas appartiennent à la série étudiée par DURAND.

Pour cette étude est considéré comme prématuré (immaturé) tout enfant ayant à la naissance un poids égal ou inférieur à 2500 g. Nous suivons ainsi la définition adoptée par l'Organisation Mondiale de la Santé.

Dans tous les cas le diagnostic de S.H.P. a été posé après un examen radiologique montrant la rétention gastrique et surtout l'existence d'un canal pylorique retréci et long tel qu'il a été décrit par MEEUWISSEN et SLOOFF, RUNSTRÖM et WALLGREN.

Sur un total de 703 cas on trouve ainsi 17 prématurés, soit 2,42 %. Ceci représente environ la moitié du nombre des prématurés par rapport aux enfants nés à terme en Suède (5 à 6 %). Il serait dangereux, vu la longueur de la période étudiée — 22 ans — et la diversité des localités d'où proviennent ces cas de faire un calcul précis du nombre de prématurés en vie après

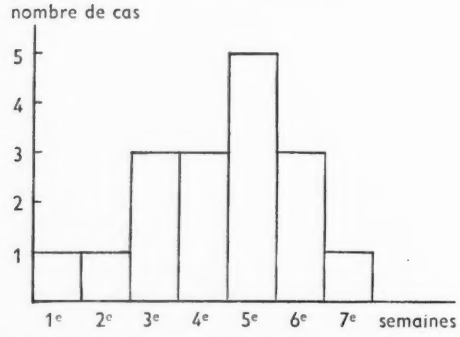

Fig. 1. Age auquel ont apparu les premiers vomissements typiques chez 17 prématurés.

un mois. Il semble toutefois que la différence qui existe entre le nombre d'enfants nés prématurément et le nombre de prématurés atteint de S.H.P. ne puisse être influencée uniquement par la mortalité qui frappe le prématuré pendant l'intervalle libre, c.-à-d. le premier mois de la vie. Plusieurs auteurs ont trouvé des chiffres assez semblables aux nôtres. FAXÉN parle de 3 nourrissons pesant 2500 g sur un total de 126 cas de S.H.P., soit 2,38 %. KAPLAN et DOBROWOLSKI décrivent 7 cas sur 222, soit 3,15 % et LEVI 5 cas sur 138, soit 3,62 %.

La distribution par sexe est identique chez les nourrissons prématurés et chez le total des enfants nés à terme : 703 cas : 559 garçons = 79,5 %, 144 filles = 20,5 %; 17 prématurés 14 garçons = 82 %, 3 filles = 18 %.

Considérant la place de l'enfant dans la famille les 17 enfants prématurés se répartissent comme suit : Premier enfant 11. Deuxième 3. Troisième 1. Quatrième 1. Septième 1.

On trouve la même prédominance chez le premier né prématuré que chez l'enfant né à terme.

Le *poids de naissance* était de

1600 g à 2000 g : 4 garçons, 2 filles, soit 6 cas.
2010 g à 2500 g : 10 garçons, 1 fille, soit 11 cas.

Dans aucun cas un autre membre de la famille n'avait été atteint de S.H.P.

Le *début de la maladie* a été dans 15 cas progressif et caractérisé par des vomissements initialement insignifiants qui devenaient ultérieurement typiques. Dans 2 cas (Obs 7 et 17) les vomissements étaient d'emblée importants et fréquents.

L'âge du début de la maladie (c.-à-d. date des premiers vomissements abondants après et entre les repas) est donné dans la Figure 1. Dans un cas (Obs 7) l'enfant a commencé à vomir abondamment dès le lendemain

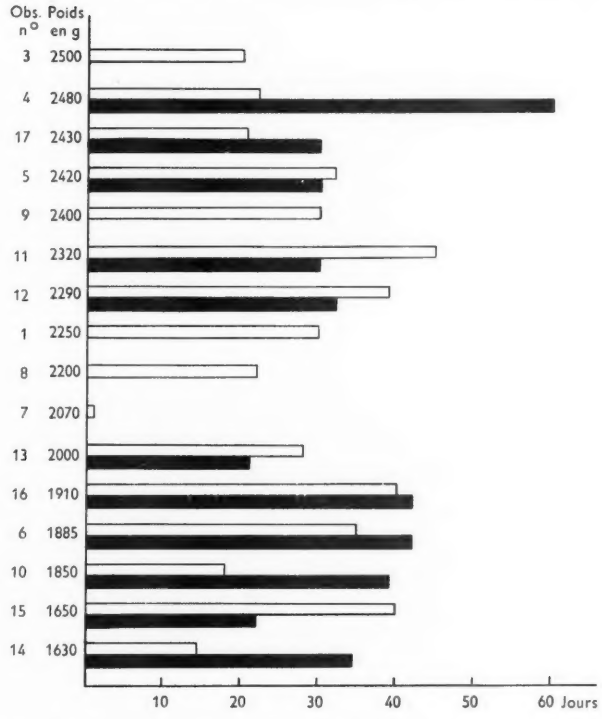

Fig. 2. Longueur de l'intervalle libre et importance de la prématuration chez 16 prématurés.

intervalle libre
importance de la prématuration.

de sa naissance. Chez 14 nourrissons, soit 82 %, la maladie débute entre la troisième et la sixième semaine de la vie, ce qui correspond à l'intervalle libre du nourrisson né à terme.

Pour 15 cas nous disposons de renseignements concernant la date présumée de l'accouchement. Nous pouvons ainsi connaître, malgré certaines erreurs qu'apporte cette méthode, l'importance de la prématuration. Chez 6 nourrissons le début de la maladie se situe à une date antérieure à celle où aurait normalement dû avoir lieu la naissance. Dans 4 cas les premiers symptômes seraient apparus pendant la première semaine de la vie. La Figure 2 illustre bien ces faits.

Ceci semble indiquer que certains facteurs postnataux agissant de la même façon chez le prématuré que chez l'enfant né à terme, sont indispensable à la manifestation de la maladie. L'intervalle libre n'est pas influencé par le poids de l'enfant ni par l'importance de la prématuration.

Symptomatologie de la S.H.P. chez le nourrisson prématuré

Les vomissements en jet ont apparu dans 10 cas, chez 7 enfants ils étaient absents. Quatre de ces derniers avaient un poids de naissance supérieur à 2000 g. Ce symptôme important peut donc faire défaut dans de nombreux cas et son absence n'est pas seulement observée chez le petit prématuré.

La constipation a été notée dans 9 des 17 cas. Comme chez l'enfant né à terme elle n'existait que pendant la période des vomissements.

L'appétit était bon dans 12 cas, chez un nourrisson il était même vorace (Obs 8). Cinq nourrissons avaient mauvais appétit. Un de ceux-ci (Obs 14) a dû être alimenté à la sonde depuis sa naissance et pratiquement pendant toute la durée de son hospitalisation. Ceci contraste avec l'appétit excellent de l'enfant né à terme qui se comporte comme un petit affamé.

La présence d'ondes péristaltiques a été remarquée chez 13 nourrissons. Dans 3 cas on les a décrit comme fortes; il s'agissait de nourrissons pesant à ce moment plus de 2800 g. Jamais des ondes péristaltiques n'ont été aperçues chez 3 nourrissons. Enfin chez un enfant on ne les a pas recherchées. Ce symptôme considéré par certains comme pathognomonique est donc moins constant chez le prématuré que chez l'enfant né à terme. Encore faut il faire le diagnostic différentiel avec les ondes physiologiques rencontrées fréquemment chez le prématuré vu la minceur de la paroi abdominale.

L'olive pylorique n'a été recherchée qu'incidemment. Sa palpation était certaine dans un cas, incertaine dans un autre (Obs 1). Pour plusieurs auteurs d'ailleurs ce symptôme n'a qu'une valeur diagnostique restreinte.

Comme il est dit plus haut, un *examen radiologique* a été fait chez tous les nourrissons et c'est sur le résultat de cet examen qu'a été établi le diagnostic de S.H.P. Dans 15 cas on a obtenu l'image d'un canal pylorique retréci, allongé et rigide; dans un de ces cas déjà à l'âge de 5 jours (Obs 7). Dans un cas on n'a pas obtenu une image satisfaisante du canal pylorique, mais il existait une forte rétention gastrique et un arrêt du péristaltisme avant le pylore. Enfin dans un cas où on ne pouvait pas voir le canal pylorique on trouva à l'opération une olive pylorique typique.

Seize enfants avaient un retard d'évacuation gastrique important. Chez un enfant (Obs 12) présentant une image typique de canal pylorique long et retréci, la baryte passait la région du pylore après 10 minutes; l'enfant avait d'ailleurs tous les symptômes de S.H.P. Des cas semblables ont été décrit par MEEUWISSEN et SLOOFF.

Diagnostic : Il sera plus difficile chez l'enfant prématuré que chez l'enfant né à terme le tableau clinique, sous lequel se présente la S.H.P. chez le prématuré, étant souvent incomplet. On trouvera dans le Tableau I la fréquence de symptômes importants dans nos 17 cas.

Tableau d'ensemble des 17 cas.

TABLEAU I

Tableau d'ensemble des 17 cas.

Observation n°	Sexe	Poids de naissance en grammes	Degré de la prématuration en jours	L'âge en jours du début de la maladie	Vomissements en jet	Ondes péristaltiques	Traitement	Durée de l'hospitalisation en jours	Evolution
1	M	2250	0	30	+	+ +	Eumydrine	114	lentement favorable
2	F	2300	?	34	–	+	Eumydrine	17	rapidement favorable
3	M	2500	0	20	+	+	Eumydrine	50	favorable
4	M	2480	60	22	+	+	Eumydrine	47	favorable
5	M	2420	30	32	+	+	Eumydrine	58	favorable
6	M	1885	42	35	+	+	Skopyl	77	favorable
7	M	2070	0	1	–	–	Eumydrine	35	rapidement favorable
8	M	2200	0	22	–	–	—	32	rapidement favorable
9	M	2400	0	30	–	–	Skopyl	113	favorable
10	M	1860	39	16	+	+	Skopyl	48	favorable
11	M	2320	30	45	+	+ +	Skopyl	18	rapidement favorable
12	M	2290	32	39	–	+	Atropine	64	favorable
13	F	2000	21	28	+	+	Skopyl	18	rapidement favorable
14	M [1]	1630	34	14	–	+	Opéré	64	décés
15	M	1650	22	40	+	+	Eumydrine	49	rapidement favorable
16	F	1910	42	40	–	+	Eumydrine	59	favorable
17	M [1]	2430	30	16	+	?	Eumydrine	73	lentement favorable

[1] Jumeau bivitellin.

La moitié des cas ainsi qu'on peut le voir avait une symptomatologie classique de S.H.P. Deux des trois cas ne présentant ni vomissements explosifs ni ondes péristaltiques étaient des formes frustes (Obs 8 et 9). Chez le troisième vomissant dès le lendemain de sa naissance on posa le diagnostic de syndrôme adréno-génital, qui ne fût pas confirmé par la suite.

Etat général à l'admission. Si on ne tient pas compte de cinq nourrissons admis pendant les deux premiers jours de la vie à cause de débilité congénitale, on constate que l'état général de douze nourrissons se répartit comme suit : bon : 2; moyen (maigre, pas déshydraté) : 4; mauvais (très maigre, très déshydraté) : 6. Parmi les 6 nourrissons en mauvais état général figurent 4 nourrissons ayant à l'admission un poids inférieur à celui de naissance.

Traitement. Un enfant a subi l'opération de Ramstedt après échec du traitement à l'eumydrine, puis au skopyl. Chez un autre enfant vomissant légèrement, les vomissements ont cessé spontanément au cours de l'hospitalisation. Pour les quinze cas restants le traitement a été, comme suit : Traitement à l'eumydrine (methylatropine employée ici en solution alcoolique) : 9 cas; traitement au skopyl (nitrate de methylscopolamine) : 5 cas; traitement à l'atropine : 1 cas.

Vu leur état de déshydratation plusieurs nourrissons reçurent des solutions de glucose ou de Ringer en hypodermoclyse.

La durée moyenne de l'hospitalisation était de 51,5 jours. Ne tenant compte toutefois que du nombre de journées passées à l'hôpital à cause de la S.H.P. — 4 nourrissons ont été admis pendant l'intervalle libre — on trouve une moyenne de 43,4 jours. Ceci se laisse comparer avantageusement avec les chiffres correspondant au traitement médical de l'enfant né à terme; qui sont 65 jours dans la série de ROHMER, et 55 à 75 jours pour celle de DURAND. La plus courte période d'hospitalisation était 17 jours, la plus longue 113 jours. Six enfants ont reçu un traitement d'entretien à domicile.

L'évolution de la courbe pondérale à partir de l'institution du traitement était nettement favorable pour la moitié des enfants, qui avaient gagné en moyenne 150 g pendant la première semaine. Les autres reprirent du poids après 2 à 5 semaines. Un enfant avait un poids stationnaire pendant plus d'un mois; il a été opéré par la suite.

Mortalité. Un enfant n'ayant pas réagi au traitement médical a été opéré alors qu'il se trouvait dans un état de dénutrition extrême. Il est décédé quelques jours après l'opération. Son décès semble devoir être imputé à son état précaire lors de l'opération.

On trouve d'ailleurs dans la littérature de nombreux cas de pyloromyotomies pratiquées avec succès même chez le petit prématuré.

Conclusion

La sténose hypertrophique du pylore est probablement moins fréquente chez le nourrisson prématuré que chez l'enfant né à terme. L'intervalle libre étant aussi long chez le prématuré que chez l'enfant né à terme, on peut supposer que même au cas où l'hypertrophie musculaire serait congénitale des facteurs postnataux doivent intervenir pour que la maladie se manifeste. La symptomatologie de la S.H.P. chez le prématuré est souvent incomplète et est souvent caractérisée par des formes atypiques et abortives. L'examen radiographique de l'évacuation gastrique et surtout du canal pylorique est indispensable pour poser un diagnostic exact. Un traitement médical bien conduit peut avoir autant de succès et ne durera en général pas plus longtemps que chez un enfant né à terme. En cas d'échec de ce traitement il faudra faire appel précocement au chirurgien.

Je tiens à remercier ici le Professeur N. Malmberg et le Dr I. Alm de l'amabilité qu'ils ont eu de mettre à ma disposition les dossiers qui se trouvent à l'Hôpital Samariten et l'Hôpital Sachs.

Résumé

Parmi 704 cas de sténose hypertrophique du pylore chez le nourrisson l'auteur a trouvé 17 cas chez des enfants ayant un poids de naissance égal ou inférieur à 2500 g et devant donc être considérés comme prématurés. Les 17 cas correspondent à 2,42 % du total des cas, ce qui représente la moitié du nombre des prématurés par rapport aux enfants nés à terme. Cette différence ne semble pas pouvoir s'expliquer par la mortalité du prématuré pendant l'intervalle libre de la sténose hypertrophique du pylore, c.-à-d. le premier mois de la vie. La distribution par sexe était la même chez les prématurés et le total des cas, soit 80 % garçons et 20 % filles.

L'intervalle libre était, pour 14 des 17 prématurés, de 3 à 6 semaines. Chez 6 prématurés la maladie a commencé à une date antérieure à la date présumée de l'accouchement. Ceci semble indiquer que chez le prématuré comme chez l'enfant né à terme certains facteurs intervenant après la naissance sont indispensables à la manifestation de la maladie.

Le tableau clinique de la S.H.P. chez le prématuré était incomplet dans 8 des 17 cas, les vomissements en jet ou les ondes péristaltiques faisant défaut. Les vomissements en jet n'ont pas apparut chez 7 prématurés.

L'examen radiologique a montré un canal pylorique retréci et allongé ainsi qu'un retard d'évacuation gastrique dans 15 cas. Dans un cas on a trouvé un arrêt du péristaltisme dans la région pylorique et une rétention gastrique. Enfin dans un cas ne montrant qu'une rétention gastrique une olive pylorique typique a été trouvée à l'opération.

Seize enfants ont été traités médicalement, à l'eumydrine, au skopyl ou à l'atropine. La durée moyenne de l'hospitalisation à cause de la S.H.P. a été 43,5 jours. Un nourrisson a été opéré après échec du traitement médical alors qu'il se trouvait dans un état de dénutrition extrême et est décédé quelques jours plus tard.

Hypertrophic Pyloric Stenosis in Premature Infants.

Out of 704 cases of hypertrophic pyloric stenosis the author has found 17 cases in prematures with a birth weight of 2500 g or less. These 17 cases correspond to 2,42 per cent of the total number of cases, which represents about one-half of the percentage of prematures at birth. The author believes that this difference cannot be satisfactorily explained by the increased mortality of premature babies during the first few weeks of life. The sex distribution is the same in the premature group as in the full-term group. The free interval after birth before projectile vomiting began was 3–6 weeks in 14 prematures. In 6 prematures the disease started at a date earlier than that of the expected date of delivery. This is believed to indicate that in the premature, as well as in the full-term baby, there are certain factors effective after birth that are necessary for the development of the disease. In 8 of the premature infants there was no projectile vomiting and no visible peristaltic waves. In 15 cases the roentgen examination showed a typical picture, in 1 case the peristalsis stopped at the proximal end of the pyloric canal, and in another, the hypertrophic muscle was found at operation.

Hypertrophische Pylorusstenose bei Frühgeburten.

Unter 704 Fällen von hypertrophischer Pylorusstenose hat der Verfasser 17 Fälle von Prematuren mit einem Geburtsgewicht von 2500 g oder weniger gefunden. Diese 17 Fälle entsprechen 2,4 % der gesamten Anzahl der Fälle, was ungefähr die Hälfte des Prozentsatzes von Prematuren bei der Geburt ausmacht. Der Verfasser glaubt, dass dieser Unterschied nicht zufriedenstellend durch die erhöhte Sterblichkeit von Frühgeburten während der ersten Lebenswochen erklärt werden kann. Die Verteilung auf die Geschlechter ist dieselbe in der Prematurengruppe und in der Gruppe der reifen Säuglinge. Der freie Intervall nach der Geburt und vor dem Beginn des Strahlerbrechens betrug 3–6 Wochen bei 14 Prematuren. Bei 6 Prematuren begann die Krankheit vor dem Zeitpunkt der erwarteten Geburt. Dies wird als Zeichen dafür angenommen, dass bei Prematuren wie auch bei reifen Säuglingen gewisse Faktoren nach der Geburt im Spiele sind, die für die Entwicklung der Krankheit notwendig sind. Bei 8 der Frühgeburten bestand kein Strahlerbrechen und keine sichtbaren peristaltischen Wellen. Bei 15 Fällen zeigte die Röntgenuntersuchung ein typisches Bild, in einem weiteren Fall kam es zu Peristaltikabbruch am proximalen Ende des Pyloruskanales und in einem anderen Fall wurde ein hypertrophischer Muskelring bei der Operation gefunden.

Estenosis pilórica hipertrófica en prematuros.

En 704 casos de estenosis pilórica hipertrófica el autor ha encontrado 17 casos de prematuros con un peso al nacer de 2500 g o menos. Estos 17 casos corresponden al 2,42 % del número total de casos, que representan a su vez la mitad del número de prematuros. El autor piensa que esta diferencia no puede ser explicada por el aumento de mortalidad de los prematuros durante las primeras semanas de vida. La distribución por sexos es la misma en el grupo de prematuros que en el grupo de nacidos a término. El intervalo entre el nacimiento y los vómitos en proyectil es de 3 a 6 semanas en los prematuros. En 6 prematuros la enfermedad comenzó antes de lo que debiera esperarse por su edad. Esto estaría a favor de la suposición de que en los prematuros, así como en los nacidos a término, hay ciertos factores posteriores al nacimiento que son necesarios para el desarrollo de la enfermedad. En 8 de 14 pre-na-

turos no había vómitos en proyectil ni ondas peristálticas visibles. En 15 casos el examen radiológico mostró un cuadro típico, pero en un caso la peristalsis se detuvo en el extremo proximal del canal pilórico y en otro se encontró un músculo hipertrófico en la operación.

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Reçu le 1 dec. 1954

Burgdam, 79
Ninove
Belgique

Acta Paediatrica 44: 272—278. May 1955

From the Children's Hospital, University of Helsinki
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Auricular Flutter in Infancy

by B. LANDTMAN and EILA KASSILA

Auricular flutter is rare in infancy. In 1950, LEACH and GIBSON found reports of only six cases of this arrhythmia in infants under one year of age. To this number they added one case of their own. A review of the literature has revealed solitary additional cases (MANNHEIMER 1940, HEDBERG 1945, LANDTMAN 1947, and MCLEAN 1952). In nine of these cases, a normal rhythm was restored. The case reported herein not only adds to the small number of cases previously described but presents some unusual features, inasmuch as the flutter persisted over a period of observation of nine months.

Case Report

The patient, a $4^1/_2$-month-old female infant, was admitted to the Children's Hospital on April 12, 1954.

Past history.—The patient was the youngest of four children. One sibling had died at the age of four months of congenital heart disease, which was proved at autopsy. The parents and the living siblings were in good health. The mother had had a mild rash, suggestive of rubella, but this happened in the eighth month of gestation. Except for this, her health had been excellent throughout the pregnancy. Prior to the delivery, the attending midwife told the mother that the fetal heart rate was "unusually rapid". The delivery, which took place at the expected time, was normal. The birth weight was 3,600 g. The neonatal period was said to have been uneventful. BCG vaccination was performed on the second day. Breast feeding was begun. The infant, however, took the breast poorly, and at the age of six weeks had gained only 200 g, and supplementary feeds were initiated. At the same time, slight respiratory distress appeared which was particularly noticeable during feedings. The feeding difficulties gradually increased and because of this the patient was brought to a physician at the age of $4^1/_2$ months. The patient was referred to the Children's Hospital with a diagnosis of congenital heart disease.

Physical Examination.—The general condition of the infant was poor. The weight was 4,770 g, and the height, 61 cm. The skin was pale and there was slight cyanosis of the lips. Moderate respiratory distress was noted; at rest, the respiratory rate was 50. The temperature was 36.8° C. Râles, suggestive of pneumonia, were audible over the left lung base. The heart rate was approximately 200 beats per minute. The heart was enlarged to percussion and the apex beat was felt at the left axillary line. The

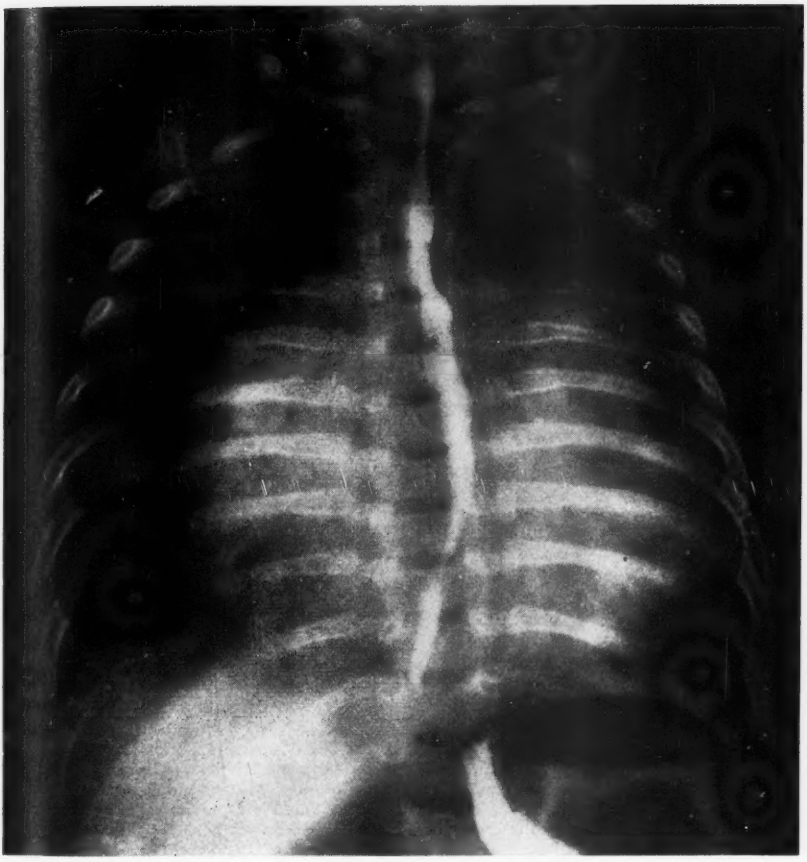

Fig. 1. Chest X-ray of an infant, 4 1/2 months of age, with persistent auricular flutter. Marked, generalized enlargement of the heart. There was no positive evidence of associated cardiac malformation.

heart sounds were snapping and the second pulmonary sound was accentuated. No murmurs were heard. The femoral pulsations were strong and symmetric. There was slight engorgement of the cervical veins. The liver was felt 3 cm below the costal margin. The remainder of the physical examination was negative.

Chest X-ray revealed marked general enlargement of the heart. The cardiothoracic index was 82 per cent. The hilar vascular markings were slightly increased but no pulsations were seen. There were no clear signs of pneumonia (Fig. 1).

The electrocardiogram showed a heart rate of approximately 200 beats per minute and auricular flutter with a 2:1 heart block (Fig. 2). The phonocardiograms are illustrated in Fig. 3.

Laboratory studies.—Hemoglobin 11.6 g; red blood cells 4,170,000; white blood

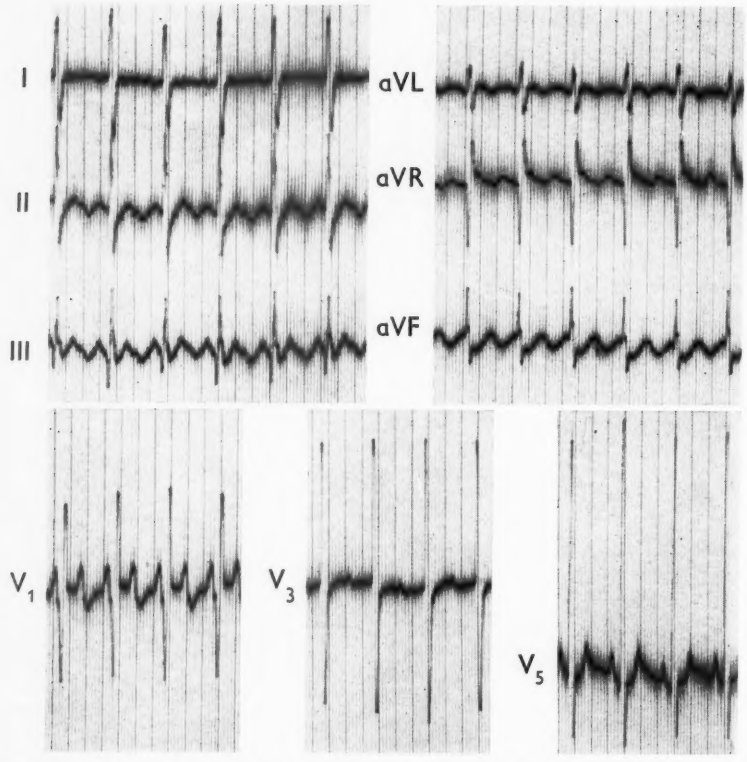

Fig. 2. The electrocardiograms show auricular flutter with 2:1 heart block. The auricular rate is 400 and the ventricular rate, 200 beats per minute. The auricular waves are clearly visible, particularly in leads V_1, V_5, II, III and aVF. There is a partial right bundle branch block and evidence of bilateral strain on the heart.

cells 15,000, sedimentation rate 3 mm. Urine examination showed albuminuria and glucosuria, and scattered white cells were seen on smear. The tuberculin patch test was positive.

Course.—Cedilanid therapy was instituted with 3 drops twice a day. Prostigmin, 0.5 cc, was given on two occasions after admission. On April 16, the dose of Cedilanid was increased to 5 drops twice a day, on May 16, to 5 drops three times a day, and on June 22, to 7 drops three times a day. In June, on two subsequent days, 0.2 mg of Cedilanid was given by intravenous injection. Quinidin sulphate, 0.1 g three times a day, was administered for one week in May. In July the patient was given Procainid half-tablet four times a day for two weeks. Despite of the treatment given, the auricular flutter and the ventricular rate remained unchanged. On a few occasions, and not associated with any particular treatment, the electrocardiogram showed a 3:1 and 4:1 block alternating with the basic 2:1 ventricular response.

Otherwise, the treatment of the patient followed standard pediatric procedures. Antibiotics were given on several occasions. The condition of the patient remained

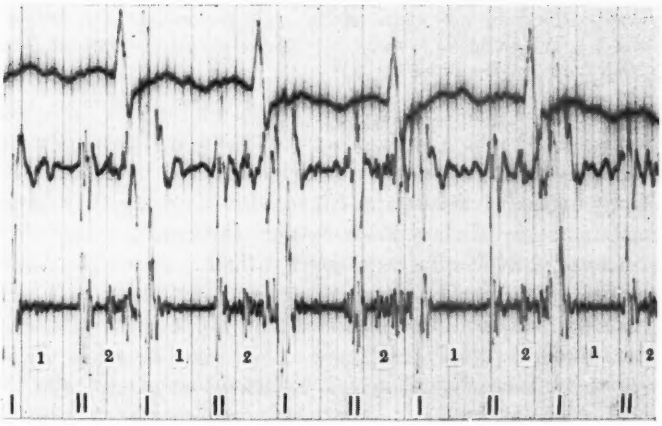

Fig. 3. Phonocardiograms (lower tracings) recorded simultaneously with the electrocardiogram (lead II). The microphone was placed over the midprecordium. The first (I) and second (II) heart sounds are accentuated. Note the marked presystolic extra sound (2). In ventricular systole, there is an extra sound (1) consisting of irregular vibrations of small amplitude. The extra sounds coincided with the auricular waves in the electrocardiogram. No pathologic murmurs are registered.

poor. Occasionally, there was a slight rise in temperature. The respiratory distress persisted and it was particularly noticeable during feedings. The size of the heart and that of the liver remained unchanged. Since there were no episodes of acute failure it was ultimately deemed feasible to continue the treatment at home. The patient was discharged on August 12, 1954, and the parents were advised to return after one month. On discharge from the hospital, the infant weighed 5,750 g.

The patient was re-admitted to the Children's Hospital at the age of 10 months, on September 13, 1954. The weight was 6,070 g and the length, 69 cm. In the interim at home, the infant had been given Cedilanid 5 drops twice a day. The clinical findings were unchanged from those described above. X-ray examination showed a cardiothoracic ratio of 80 per cent. Repeated electrocardiographic studies revealed auricular flutter with a 2:1 block and a ventricular rate of approximately 200 per minute. No pathologic murmurs were registered in the phonocardiogram. The blood picture, including differential count, was normal. Urinalysis yielded, as before, scattered white cells. Additional laboratory studies were as follows: Serum protein, 5.0 g per cent; plasma chlorides, 362 mg per cent; plasma potassium, 18.4 mg per cent; plasma sodium, 135 mg per cent; alkali reserve, 53 vol. per cent; and blood urea, 31 mg per cent.

The patient was discharged from the hospital on September 23, 1954. At that time, the weight was 5,900 g.

By agreement, the parents returned with the patient to the Children's Hospital on November 30, 1954. The patient was then 1 year and 10 days of age. At home, the condition of the child had remained unchanged. Cedilanid had been given, 5 drops twice a day. The weight was 6,700 g. Physical examination, supplemented by X-ray, electrocardiographic and phonocardiographic studies revealed, except for a mild upper respiratory infection, exactly the same findings as on the previous admissions. As be-

fore, the ventricular rate was approximately 200 per minute and the ventricular response was 2:1. The blood count and the urinary findings were normal. The patient was sent back home on December 9, 1954.

Discussion

Although the auricular flutter was not diagnosed by means of electrocardiography until the patient was $4^1/_2$ months of age, the case history and the persistent nature of the flutter strongly favoured a congenital origin. Solitary cases of auricular flutter present at birth, or even prenatally, have been reported by different authors (CARR and MCCLURE 1931, HEDBERG 1945, STADLER 1948, and MCLEAN 1952). In all of these cases, a normal rhythm was restored.

There is still a lack of agreement as to the cause of auricular flutter in infants and older children. Some authors have discussed its possible association with congenital heart disease (AMBERG and WILLIUS 1926, CALO 1939, HALBERTSMA and HARTOG 1939, and PRINCE and ROTONDO 1946). In most of the cases described, however, there has been no apparent underlying cause. In the present case, there was no positive evidence of associated congenital malformations of the heart. No pathologic murmurs were registered. Moreover, the enlargement of the heart and the changes in the electrocardiogram could have been due to the cardiac failure without there being associated structural defects.

The mode of origin of auricular flutter is only imperfectly understood. According to the "circus movement" theory, this arrhythmia is explained as a rapid circulating wave of excitation in the auricular wall (LEWIS 1925, and others). Recently, however, experimental and clinical observations have given strong support to the opinion, expressed by many observers, that auricular flutter is caused by a rapid stimulus formation originating in one or more ectopic foci in the auricular muscle (HEJTMANCIK *et al.* 1950, PRINZMETAL *et al.* 1950, and SHERF *et al.* 1953). If this last-mentioned theory is correct, it is possible that, in the present case, the action of the heart was governed by such an ectopic focus, the sinus node being non-functioning. The possibility, however, of the sinus node being capable of an unusually rapid rate of stimulus formation may, perhaps, also be borne in mind.

There seems to be little doubt that the fluttering auricles were in some way responsible for the extra sounds recorded in the phonocardiogram. Auricular sounds occurring synchronously with the P wave in the electrocardiogram have been recorded in adult patients with auricular flutter (HECHT and MYERS 1945, and BIEHL and SIMON 1953). In most of the cases described the ventricular rate was less than 100. In the present case,

the ventricular rate was approximately 200 which made a recording of heart sounds more difficult. It was noted that the amplitude of the extra sound, occurring in presystole, was much greater than that of the extra systolic sound. HECHT and MYERS 1945, have made the same observation in their studies of two adult patients with auricular flutter. In fact, they claimed that their cases were the only ones on record in which auricular sounds of the fluttering auricle could be registered during systole.

The treatment of auricular flutter in infants and older children is often unsatisfactory. Digitalis and quinidine have been tried, occasionally with good result. On the other hand, there are cases described in which a normal rhythm has spontaneously been resumed (CALO 1939, and HOYER and LYON 1946). In the present case, no effect was obtained by digitalis or quinidine, although the doses used were much higher than in cases previously successfully treated with these drugs.

The outlook of long-lasting auricular flutter in infants is poor. Of the two cases described, both had a fatal outcome within the first year of life (CALO 1939, and LANDTMAN 1947). It was somewhat surprising that the clinical signs of failure were not more pronounced in the present case despite the ventricular rate of 200 persisting over a period of 9 months.

Summary

A case of persistent auricular flutter in an infant is reported. The arrhythmia was diagnosed by means of electrocardiography when the patient was $4^1/_2$ months of age. The case history and the persistent nature of the flutter strongly favoured a congenital origin. There was no positive evidence of associated malformations of the heart. Treatment with digitalis, quinidine, Procamide and Prostigmin had no effect. A total of 34 electrocardiographic examinations, supplemented by phonocardiographic studies, were performed during a period of observation of 9 months. The ventricular rate remained approximately at 200 and there was a 2:1 ventricular response. The patient was last seen at the age of 1 year and 3 weeks.

Flutter auriculaire chez le nourrisson.

L'auteur rapporte un cas de flutter auriculaire persistant chez un nourrisson. Le diagnostic de l'arythmie a été posé à l'âge de quatre mois et demie grâce à l'électrocardiogramme. L'histoire de la maladie et la persistance du flutter étaient des arguments importants en faveur d'une origine congénitale. On n'a pas trouvé de signes certains d'une malformation cardiaque associée. Un traitement à la digitaline, la quinidine, la procamide et la prostigmine n'avait aucun effet. Le rythme ventriculaire restait aux environs de 200 avec une réponse du ventricule de 2:1. Le patient a été vu une dernière fois à l'âge d'un an et trois semaines.

Vorhofflattern im Kindesalter.

Ein Fall eines andauernden Vorhofflatterns bei einem Kind wird besprochen. Die Arrhythmie wurde im Alter von $4^1/_2$ Monaten bei dem Kinde mit Hilfe des EKG dia-

gnostiziert. Die Krankengeschichte und das Persistieren des Flatterns sprechen streng für eine kongenitale Genese. Es gab kein positives Zeichen für gleichzeitige Missbildungen des Herzens. Die Behandlung mit Digitalis, Chinidin, Procamid und Prostigmin hatte keinen Effekt. Die Kammerfrequenz blieb annähernd 200 bei einem 2:1 Block. Der Patient wurde zuletzt im Alter von 1 Jahr und 3 Monaten gesehen.

Aleteo auricular en lactantes.

Se refiere el caso de un aleteo auricular persistente en un lactante. El transtorno del ritmo fué diagnosticado por medio del electrocardiograma cuando el paciente tenía cuatro meses y medio de edad. La historia del caso, y la persistencia del transtorno están fuertemente a favor de su origen congénito. No había señales positivos de malformación asociada del corazón. El tratamiento con digital, quinidina, procainamida y prostigmina no dieron resultado. La frecuencia ventricular permaneció aproximadamente en 200 y había una respuesta ventricular de 2:1. El paciente fué visto la última vez con la edad de un año y tres semanas.

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Received Jan. 13, 1955

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Acta Pædiatrica **44**: 279—286. May 1955

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Osteogenesis Imperfecta Associated with Ehlers-Danlos Syndrome

by AXEL BIERING *and* TORBEN IVERSEN

The combination of osteogenesis imperfecta and the Ehlers-Danlos syndrome in the same patient does not seem to have been reported before. KANOF (15) described a patient with Ehlers-Danlos syndrome, blue sclerae and osteoporosis, but without fractures. In the discussion following JOHNSON and FALLS' paper on Ehlers-Danlos syndrome (14), JOHNSON said: "In osteogenesis imperfecta (fragilitas ossium) one may also find hyperextensibility of the joints. The blue scleras and history of repeated fractures should help one to differentiate this condition from the Ehlers-Danlos syndrome. These changes will be looked for in future cases of the Ehlers-Danlos syndrome."

In the Department of Paediatrics of the Rigshospital, Copenhagen, we have seen a patient who presented both osteogenesis imperfecta and the Ehlers-Danlos syndrome.

Case Report

A boy, G. C., born on Jan. 23, 1951.

History.—The patient was the younger of two children. There was no consanguinity. The father's skin was more freely movable over the underlying structures than normal and could be picked up in folds on the trunk and extremities. Otherwise his skin appeared normal, and there was no bleeding tendency. The proximal phalangeal joints of the fingers and toes showed some hyperextensibility. The paternal grandmother and several other members of the family in the paternal line had also hyperextensible joints. There was no history of increased fragility of bone, blue sclerae or deafness of unknown cause in the family. The pregnancy and delivery had been normal; birth weight 3,600 g, length 53 cm.

From birth the patient's skin had been wrinkled and loose, and excessive laxity of the joints was noted. Spontaneous movements of the legs were almost absent. At the age of 5 months he was admitted to the Orthopaedic Hospital, Copenhagen, for bilateral dislocation of the hip. Arthrography showed complete dislocation of both hip joints, but the range of movement was nevertheless unimpaired on both sides. In addition, subluxation of both knee joints and numerous fractures of the thoracic and lumbar vertebrae were revealed. During the hospital stay spontaneous fractures

Fig. 1. Photograph of patient, 2 years old, showing the peculiar facial expression, the wrinkled skin and the dislocation of the hips.

of both femoral necks just below the epiphyseal lines occurred, and enormous subperiosteal haematomata extending to the distal epiphyseal lines developed. The femoral fractures were treated with zinc-oxide-gelatin dressing and traction-suspension, following which enormous callus formation developed on both sides. At the age of 11 months the patient was admitted to the Department of Paediatrics of the Kigshospital.

Physical examination.—The patient was very limp; he was unable to raise his head when placed in the dorsal position; he could not sit without support and did not attempt to stand. When the patient was placed in the sitting position, pronounced thoracic kyphosis was seen. He was able to hold up his head when placed in the sitting position. He could smile and fix his gaze on objects and could grasp them, and he responded to sounds. The skin was pale with a conspicuous venous network; it was markedly wrinkled, seemed too large, and was freely movable over the underlying tissue, from which it could be picked up in folds (Figs. 1 and 2). There were no ecchymoses, scars or abnormalities of the nails, and hair growth was normal. The skull was rather high, but otherwise of normal configuration, the cranial circumference being 44.5 cm. The anterior fontanelle measured 5 × 6 cm, and the cranial

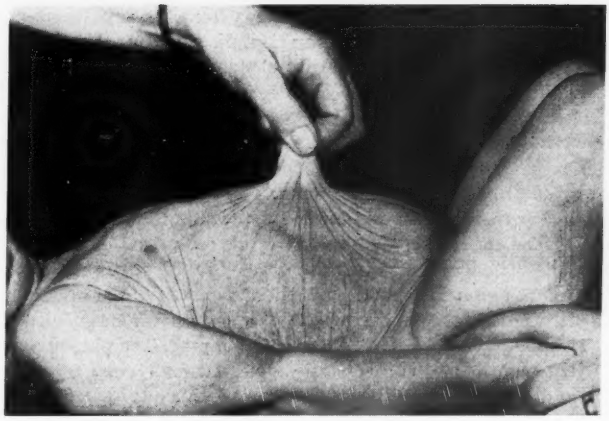

Fig. 2. Another photograph of patient, at the age of 2 years, showing the excessive elasticity of the skin.

bones were soft. The flat nasal bridge, the somewhat prominent eyes with bluish sclerae and the open mouth with the protruding tongue gave the patient a peculiar facial expression. The external ears were of normal appearance. The palate was high, without defects. The mesial teeth were in eruption. The extremities were limp and hypotonic with pronounced hyperextensibility of all joints, particularly those of the wrists, fingers and ankles. There was subluxation of both knee joints. The fingers could be hyperextended parallel to the forearm. He moved both arms and the left leg, while the right leg was kept fixed in abduction and flexion of the hip joint. The right thigh was markedly swollen and tender. The rest of the physical examination was non-contributory.

Laboratory findings.—A complete blood examination including tests for haemorrhagic diathesis showed normal conditions. Serum protein 7.5 g (albumin 4.8 g, globulin 2.7 g), total cholesterol 200 mg, serum calcium 10.7 mg and blood phosphorus 4.6 mg per 100 ml, serum phosphatase 77 units (Lundsteen and Vermehren). The urine was normal. The Sulkowitch test was negative. The urinary excretion of 17-ketosteroids was normal (1.1 mg per 24 hours).

Ophthalmological examination.—The eyes showed some protrusion, with large palpebral fissures, presumably due to the flat orbits. The sclerae were definitely bluish. Otherwise, no abnormalities were disclosed (P. Brændstrup).

Histological examination of a biopsy specimen of the skin showed a normal epidermis, whereas all the elastic fibres of the corium was broken up into fragments. In the stratum papillare the bundles of collagen fibres showed a somewhat loose-woven texture, while they were normal in the deeper layer. The ground substance took a slightly metachromatic stain with toluidine blue, i.e. the content of mucopolysaccharides was normal. Abundant amounts of mast cells were seen perivascularly, while the number of these cells in the connective tissue was normal. No fibrinoid degeneration; moderate oedema of the connective tissue; all lumina of the vessels were gaping (G. Asboe Hansen).

Roentgen examination of the osseous system revealed a recent fracture of the right femur 3 cm above the knee joint and residues of the aforementioned older fractures

as well as bilateral hip dislocation, which differed from the usual congenital type in that the acetabula were of normal configuration. In addition, there was an extreme generalized osteoporosis, and the markedly slender long bones were framed by a thin, sharply defined compacta. The callus formation appeared normal. The skull did not reveal definite abnormalities, and the sella turcica was normal. Roentgenographic diagnosis: osteogenesis imperfecta. *Roentgen examination of the intestinal tract* showed a markedly patchy distribution of the contrast medium and almost complete absence of a mucosal pattern in the jejunum. The contrast passed the bowel in normal time. The caecum was long and extended towards the midline. The duodenum was not dilated. The changes in the small intestine resembled those seen in enteritis.

Clinical course.—The femoral fracture was treated with adhesive-tape dressing and traction-suspension; union in a good position was obtained within normal time. Additional fractures did not occur during the hospital stay. Treatment of the osseous and cutaneous diseases of the patient was not attempted. The patient was discharged at the age of 14 months and subsequently appeared for regular follow-up examinations in the children's out-patient department up to May 1953. He could sit without support at the age of 18 months and stand alone at two years. New fractures did not occur during the observation period.

Discussion

The diagnosis of osteogenesis imperfecta must be considered unquestionable. Both the spontaneous fractures and the roentgenological findings are in favour of this diagnosis. Although not very distinct, blue sclerae were also present. According to SEEDORFF's classification (25, page 35), the case described here belongs to "typus gravis" or type II, in which the fractures occur either during delivery or in infancy.

The diagnosis of Ehlers-Danlos syndrome must also be regarded as established beyond doubt. In addition to loosely attached skin (cutis laxa sive hyperelastica) and hyperextensibility of the joints, the completely developed syndrome comprises cutaneous fragility, which following slight traumata may give rise to atrophic scar formations, sometimes with bulging of the markedly vascularized, translucent subcutis, so that angioma-like "pseudotumours" develop over the bony prominences, particularly of the elbows and knees. The tendency to ecchymoses and haematomata, which has so often been reported, is presumably also related to local conditions of the skin and to fragility of the blood vessels, since haemorrhagic diathesis due to alterations of intravascular factors of clotting has not been described.[1]

[1] However, in this department we have seen a case of Ehlers-Danlos syndrome and concurrent familial haemorrhagic diathesis with prolonged coagulation time in a six-year-old boy. The patient was admitted to hospital because of a tendency to large sugillations and subperiosteal haematomata. Physical examination revealed a moderately severe cutis hyperelastica without scars or pseudotumours and without hyperextensibility of the joints, apart from the fact that the hands, with the elbows fully extended, could be pronated 90°

Dislocation of the hip (8, 15, 23) and habitual dislocation of other joints (23) have previously been observed in the Ehlers-Danlos syndrome. The roentgenographic abnormalities of the intestines observed during the passage of the barium meal have not previously been mentioned in the literature, but several authors have reported disturbances in the motility of the alimentary tract, such as enteroptosis (21), gastric atony (1, 24), mega-oesophagus and megacolon (19).

Familial occurrence has often been observed. HUSEBYE (12) demonstrated the syndrome in four and JOHNSON and FALLS (14) in six generations, in both families inherited as a Mendelian dominant.

While cases of the Ehlers-Danlos syndrome associated with osteogenesis imperfecta have not previously been described, some cases of the Ehlers-Danlos syndrome with other bone changes have been reported. DEBRÉ and SEMELAIGNE (8) described a patient with a typical Ehlers-Danlos syndrome, in whom congenital dislocation of the hip, a very large fontanelle ("like a veritable dysostosis") and flat orbits with prominent eyes were seen, i.e. the same three anomalies as were encountered in our patient. Osteoporosis has also been reported (1, 3, 15, 20, 24), in one case accompanied by increased serum calcium (3), which has also been observed unassociated with osteoporosis (23). We have been unable to trace descriptions of direct demonstration of parathyroid disease; the case reported by PERREAU *et al.* (22) cannot be interpreted as one of the Ehlers-Danlos syndrome, as the patient was suffering from an acquired disease.

There seems to be a marked tendency to skeletal anomalies such as thoracic deformities (1, 7, 24), peculiar forms of the skull (1, 24, 28), arachnodactyly, clinodactyly (1, 24), spina bifida and absence of the ensiform process (17).

Soft-part anomalies are also frequently encountered in patients with the Ehlers-Danlos syndrome. In addition to the aforementioned abnormalities of the alimentary tract, diffuse muscular atrophy (20), congenital cardiac disease (10), acrocyanosis (1, 6, 11, 23, 24), multiple lipomata (27), neurofibromatosis (4, 26), syndactyly (13), webbed fingers and abnormalities of the external ear (1, 24) may be mentioned. Several patients with the Ehlers-Danlos syndrome have been described as oligophrenic (1, 16, 18, 24).

more than normal. Resolving sugillations were noted in several places on the trunk and extremities, but there were no recent subcutaneous bleedings. The coagulation time was 10–16.5 minutes. All other tests for haemorrhagic diathesis and a complete blood examination showed normal conditions. The mother's coagulation time was 10–15.5 minutes. Neither the mother nor any other members of the family had revealed abnormal bleeding tendencies. There were no known cases of loose skin in the family (the mother and a maternal aunt were examined while the patient was in hospital).

While, as already mentioned, osseous anomalies are frequent in the Ehlers-Danlos syndrome, there does not seem to be any special tendency to gross cutaneous abnormalities in osteogenesis imperfecta. However, BLEGVAD and HAXTHAUSEN (5) described a patient with osteogenesis imperfecta complicated by atrophia maculosa cutis, a rare skin affection which usually begins with round, slightly elevated bluish-red spots, varying in size from a lentil to a shilling; these spots are slowly transformed into atrophic areas. Elastin staining revealed atrophy of the elastic tissue. The patient had also zonular cataract. The authors assumed that the cutaneous atrophy represented a symptom parallel with the blue sclerae and the osseous changes, or that the debility of the mesodermal tissue might predispose to the development of the cutaneous atrophy. Except for eczema in one patient, they did not find descriptions of skin affections in osteogenesis imperfecta.

However, it is known that the skin in patients with osteogenesis imperfecta is very thin and delicate. BAUER (2) spoke of "eine übermässige, gummiartige Dehnbarkeit" and interpreted osteogenesis imperfecta as a systemic disease of the mesodermal tissue, because his histological studies had revealed a defective development of the fibres and greater variability in the cell forms than is normal. Apart from the most primitive connective tissue in the umbilical cord, which was without demonstrable changes, he found these abnormalities in all mesodermal tissues examined, but on an ascending scale from the more primitive forms to the highest specialized ones, viz. osseous tissue and dentine. In the subcutis the abnormalities could be demonstrated only "bei genauerem Zusehen"; the corium was not mentioned. BAUER's view is supported by the histochemical studies of FOLLIS (9), who concluded that osteogenesis imperfecta is a systemic disease of the connective tissue in certain areas consisting in a failure of reticulum fibres to differentiate into collagen fibres; at the same time it was possible to demonstrate a substance in the bones which might be conceived as an immature form of bone matrix.

Similar studies have not been reported in the Ehlers-Danlos syndrome.[1] In the discussion of the paper of JOHNSON and FALLS (14), TOBIAS stated that the pathological changes in different cases are not uniform; the amounts of both elastic and collagen fibres may be normal, increased or decreased.

Patients with osteogenesis imperfecta often show a tendency to sub-

[1] We are indebted to Dr. K. E. SJØLIN, who kindly subjected biopsy specimens of skin from two patients with the Ehlers-Danlos syndrome and osteogenesis imperfecta, respectively, and from five normal children to histological studies by the method of FOLLIS. He was unable to demonstrate the changes observed by FOLLIS in osteogenesis imperfecta.

cutaneous bleedings (25) and hypermobility of the joints (25), and a further parallelism between the two diseases in question appears in the other anomalies of the bones and soft parts frequently seen in osteogenesis imperfecta, for example, arachnodactyly, syndactyly, achondroplasia, progressive muscular atrophy and mental abnormalities (25).

The occurrence of the Ehlers-Danlos syndrome and osteogenesis imperfecta in the same patient might be a mere coincidence. However, both diseases affect mesodermal tissue and are usually conceived to be congenital malformations of connective tissue and osseous tissue, respectively. It may therefore be justifiable to interpret the case reported here as a particularly profound mesodermal malformation.

Summary

A case of the Ehlers-Danlos syndrome associated with osteogenesis imperfecta is reported. The possibilities of a pathogenetic relationship are discussed with particular reference to accompanying anomalies in the two syndromes. Simultaneous occurrence of the two syndromes has not previously been reported.

Osteogenesis imperfecta associée à un syndrome d'Ehlers-Danlos.

Description d'un cas de syndrôme d'Ehlers-Danlos associé à une osteogenesis imperfecta. Les possibilités de relations pathogéniques sont discutées, avec une mention particulière d'anomalies accompagnant ces syndrômes. La coexistence de ces deux syndrômes n'avait pas encore été décrite.

Osteogenesis imperfecta vergesellschaftet mit Ehlers-Danlos Syndrom.

Ein Fall von Ehlers-Danlos Syndrom vergesellschaftet mit Osteogenesis imperfecta wird mitgeteilt. Die Möglichkeit eines pathogenetischen Zusammenhanges wird diskutiert mit besonderem Hinblick auf die begleitenden Anomalien der Syndrome. Gleichzeitiges Auftreten der beiden Syndrome ist vorher noch nicht beschrieben worden.

Osteogénesis imperfecta asociada con el síndrome de Ehlers-Danlos.

Se refiere un caso de osteogénesis imperfecta asociada con síndrome de Ehlers Danlos. Se discuten las posibilidades de una relación patogénica con especial referencia a las anomalías que acompañan al síndrome. No se habían referido anteriormente casos de simultaneidad de los dos síndromes.

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Received Dec. 24, 1954

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Acta Pædiatrica **44**: 287—292. May 1955

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Hemihypertrophy and Wilms's Tumour

by STIG-IVAR BJÖRKLUND

The two halves of the body are relatively asymmetrical. Obviously, these differences are undetectable unless careful mensuration is employed. Gross, or readily appreciable asymmetries, are comparatively uncommon: in fact they are considered one of the most unique of all congenital developmental anomalies (BRAGMAN). Less than 120 cases have been reported in the literature (SILVER *et al.* 1953).

This asymmetry or hemihypertrophy can be partial or total, as well as crossed. True and pseudo forms of hemihypertrophy are recognized. The true cases involve the skeleton as well as the soft parts, while the pseudo-cases do not involve the bony structure.

Hemihypertrophy can only be confused with congenital hemiatrophy. Lesions of the central nervous system are known to cause hemiatrophy (WARD *et al.*). WAKEFIELD *et al.* claim that after careful neurologic examination to rule out hemiatrophy, the differential diagnosis should offer little difficulty if the possibility of hemihypertrophy is kept in mind.

The following factors have been discussed as being of possible etiologic importance: endocrine disorders, congenital syphilis, vascular lesions, abnormalities of the lymphatic system, lesions of the brain, embryonic defects of the vegetative system, mechanical influences, heredity, and embryogenic variants (WARD *et al.*). It is now widely accepted that hemihypertrophy is due to embryonic anomalies. It has also been suggested (GESELL) that hemihypertrophy is due to a deviation of the normal process of twinning, i.e., a mild gigantism of a person whose lesser somatic half is normal.

Mental deficiency is said to occur in 15–20 per cent of all cases and other, associated abnormalities in 50 per cent (WARD *et al.*): abnormal nail growth, clubbed feet, hypospadius, cryptorchism, congenital heart disease, polydactylism, syndactylism, and supernumerary nipples.

Some cases of hemihypertrophy with homolateral or contralateral adrenocortical hyperplasia are on record. RIEDEL has described a case of left-sided hemihypertrophy with adrenogenital syndrome in whom operation at 11 months revealed a non-malignant adenoma in the right adrenal

and in whom re-operation at 5 years 9 months revealed a Wilms's tumour on the right side. Judging by a fairly extensive search of the literature, this is the only case on record of hemihypertrophy in combination with Wilms's tumour. It was therefore thought that the contribution of the following two cases might be of interest.

Case 1.—The patient was a female child. Her older sister and parents were healthy. At 4 months it was noticed that the right leg was longer than the left. At 8 months the child was admitted to the hospital because of an acute respiratory tract infection. Neurologic examination revealed nothing of interest. The right leg was 2 cm longer and 2–2.5 cm larger in circumference than the left. Abdominal palpation did not disclose any signs of a pathologic condition. At 15 months the child was re-admitted because of an acute infection. Abdominal palpation now revealed a tumour on the left side. The right leg was still longer and thicker than the left. Roentgen examination of the right leg showed that the hypertrophy had involved both the soft parts and the skeleton, and urography revealed a tumour of the left kidney. At operation 14 days later a capsulated tumour, the size of a fist, was removed. Microscopic examination showed the characteristics of Wilms's tumour.

The child died 7 months later. At autopsy numerous metastases were seen in the abdomen, but not in the liver or the lungs. The suprarenals and the right kidney showed nothing abnormal.

Case 2.—The patient was a female child. Her older sister and parents were healthy. At 5 months it was noticed that the left extremities were longer and thicker than those on the right side. Neurologic examination revealed nothing of interest. The child was admitted at 4 1/2 years because of a tumour in the left part of the abdomen. She still had left-sided hemihypertrophy involving the entire body. Roentgen examination showed that both the soft tissues and the skeleton were involved. Urography disclosed that the tumour originated in the left kidney. At operation, 7 days later, a renal tumour the size of a child's head and growing through the peritoneum was removed. Microscopic examination showed the characteristics of Wilms's tumour.

The child died 4 months later. At autopsy metastases were seen in the lungs and in the liver. The right kidney and the suprarenals showed no signs of involvement.

Discussion

In the two cases described above the patients were females, both with Wilms's tumour on the left side and both with hemihypertrophy, right-sided in one and left-sided in the other.

The pathogenesis of Wilms's tumour permits only an embryonic explanation, for which many theories have been advanced. These theories differ according to the supposed time and nature of origin and localization of the anlage of the neoplasm (CAMPBELL). It has also been suggested that the tumour itself represents a malformed organ (NICHOLSON).

While hemihypertrophy is often associated with other malformations, Wilms's tumour does not appear to be so other than that the tumour-bear-

Fig 1. Case 1. The hypertrophy of the right femur, the tibia, and the fibula is evident. The hypertrophy of the soft tissues is present but not plainly visible in the picture.

ing kidney may be anomalous (CAMPBELL). Wilms's tumour has been found in reduplicated kidneys, in a congenitally solitary kidney, in a polycystic kidney, in a horseshoe kidney, and in a supernumerary renal mass attached to the capsule of the true kidney. According to HARRAH, other congenital malformations are also seen in association with Wilms's tumour, but he did not say what type of malformations, nor did he say anything about the types or frequencies of such malformations.

Fig. 2. Case 2. The left hemihypertrophy is evident. The shadowing represents the palpable tumour.

This question that logically presents itself is whether the development of Wilms's tumour in only 3 cases of 120 cases of hemihypertrophy on record should be regarded as pure coincidences, or whether this combination might, in reality, be commoner than supposed. Literature studies can give no definite answer to this question, because (*a*) not all cases of hemihypertrophy observed have been reported, (*b*) in some of those cases of

hemihypertrophy on record, Wilms's tumour might have been detected later but not described in the literature, and (*c*) in reports of Wilms's tumour any co-existent hemihypertrophy might have passed unnoticed or have been considered irrelevant and not been reported.

Wilms's tumour must be regarded as congenital. For a varying length of time, during which it may grow slowly or may be in a quiescent stage, it produces no symptoms, but in the final stage it grows rapidly. In both of the cases described above routine examination with abdominal palpation 6 months before the discovery of the tumour had revealed no signs of a pathologic condition.

In view of the observations made in the two cases under discussion, it is suggested that all children with hemihypertrophy should be examined urographically at least once every six months in order to detect the presence of any Wilms's tumour in as early a stage as possible. The other malformations described in association with hemihypertrophy are much more readily detected at routine examination and are by no means so important.

Summary

Two cases of hemihypertrophy are described, in which Wilms's tumour was afterwards diagnosed. It is suggested that all children with hemihypertrophy should be examined urographically at least once every six months in order to detect the presence of any such a tumour in as early a stage as possible.

Hémihypertrophie et Tumeur de Wilms.

Description de deux cas d'hémihypertrophie chez lesquels une tumeur de Wilms fut découverte ultérieurement. Il est suggéré de pratiquer une urographie, au moins tous les 6 mois, ches les enfants atteints d'hémihypertrophie afin de détecter aussitot que possible l'existence d'une tumeur rénale éventuelle.

Hemihypertrophie und Wilms' Tumor.

Zwei Fälle von Hemihypertrophie sind beschrieben, bei denen Wilms' Tumor später diagnostiziert wurde. Es wird vorgeschlagen, dass alle Kinder mit Hemihypertrophie durch eine Urographie untersucht werden sollten, wenigstens einmal halbjährlich, um das Vorhandensein eines solchen Tumors in einem möglichst frühen Stadium aufzuklären.

Hemihipertrofia y tumor de Wilms.

Se describen dos casos de hemihipertrofia, en los cuales posteriormente se diagnosticó tumor de Wilms. Se sugiere que todos los niños con hemihipertrofia debieran ser examinados desde el punto de vista urológico, al menos una vez cada seis meses con el fin de detectar con la mayor precocidad posible dicho tumor.

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Received Dec. 24, 1954

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Acta pædiatrica **44**: 292. May 1955

BOOK REVIEWS

Perspectives and Horizons in Microbiology. A symposium edited by S. Waksman.

Rutgers University Press, New Jersey, 1955. $ 3.15.

This symposium was held the 7th of June 1954 in connection with the dedication of the Institute of Microbiology, Rutgers University. Some of the best known workers in different fields of microbiology participated presenting current trends and inspiring perspectives. All chapters deserve to be read in detail, and only a glimpse of the content will be given here. J. Lederberg writes on "Genetics and microbiology"; H. A. Barker on "Progress and problems in bacterial metabolism"; W. Umbreit on "Metabolic pathways"; and D. Peterson on "Microorganism and steroid transformation" (a new field for practical application of microbiology).

M. Heidelberger gives a short survey of unsolved problems in immunology. F. Horsfall jr. presents encouraging experiments on the inhibition of virus reproduction by chemical substances. H. Eagle describes our lack of knowledge of the mode of action and the biology of antibiotics.

The well-printed volume concludes with an essay on the training of research workers with many intelligent quotations by S. Waksman, chief of the Institute ("Microbiology takes the stage").

This book will prove to be inspiring to physicians as well as biologists, for the broad subject of microbiology is dealt with comprehensively without going into details.

R. LAGERCRANTZ, Stockholm.